FORM PTO-1390 (REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 080056-000200US

U.S. APPLICATION NO (If known, see 37 CFR 1.5): 09/647054

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU99/00207	March 24, 1999	March 24, 1998

TITLE OF INVENTION: PEPTIDE TURN MIMETICS

APPLICANT(S) FOR DO/EO/US: PETER JOSEPH CASSIDY; PETER ALAN HUNT; PAUL FRANCIS ALEWOOD; TRACIE ELIZABETH RAMSDALE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [x] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [xx] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [x] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [x] Other items or information:

    Courtesy copy of published application
    ISR, 15 references
    IPER

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/647054	PCT/AU99/00207	080056-000200US

17. [x] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $760.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	73 - 20 =	+53	X $18.00	$954	
Independent claims	30 - 3 =	+27	X $78.00	$ 2,106	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 4,030	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$	
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 4,030	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 4,030	
				Amount to be: refunded	$
				charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [x] Please charge my Deposit Account No. 20-1430 in the amount of $ 4,030 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-1430. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Kevin L. Bastian
Townsend and Townsend and Crew LLP
Two Embarcadero Center, 8th fl.
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SIGNATURE

Kevin L. Bastian
NAME

34,774
REGISTRATION NUMBER

PATENT
Attorney Docket No.: 80056-000200US
Client Reference No.: 6279US2-RTK/NRB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. National Phase of
PCT/AU99/00207 of:

PETER ALAN HUNT, et al.

Application No.: Not yet assigned

Filed: Herewith

For: PEPTIDE TURN MIMETICS

PRELIMINARY AMENDMENT

San Francisco, CA 94111
September 25, 2000

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-referenced application, please enter the following amendments and remarks.

IN THE CLAIMS:

Claim 66, line 1, please delete "or 48".

Claim 67, line 1, delete "or 48".

Claim 73, line 2, delete "any one of Claims 1-31" and substitute therefor --Claim 1--.

REMARKS

Amendment is made to delete the multiple dependencies from claims 66, 67 and 73, thereby avoiding the need to pay the multiple dependent surcharge.

Respectfully submitted,

Kevin L. Bastian
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SF 1139279 v1

#3 C. Bunt

Applicant petitions the Commissioner of Patents and Trademarks to extend the time for response. Pursuant to 37 CFR §1.17(a)(2), please charge Deposit Account No. 20-1430 in the amount of $390 (extension of time).

The Commissioner is hereby authorized to charge Deposit Account No. 20-1430 in the amount of $135 which covers the amount due for surcharge fee.

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 20-1430. This transmittal letter is submitted in duplicate.

Respectfully submitted,

Kevin L. Bastian
Reg. No. 34,774

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TITLE

"PEPTIDE TURN MIMETICS"

FIELD OF THE INVENTION

THIS INVENTION relates to new compounds designed to be peptide turn mimetics, and to new compounds useful for the synthesis of peptide mimetics, especially turn mimetics. Peptide mimetics are used to reproduce the important structural and functional elements contained in a bio-active peptide sequence principally in order to develop novel pharmaceuticals with increased binding affinity, selectivity, stability and/or oral bioavailability compared to the bio-active peptide.

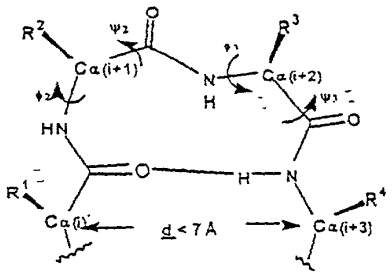
BACKGROUND OF THE INVENTION

Reverse turns (beta and gamma turns and beta bulges) are localised on the protein surface (Kuntz, 1972) and are of importance in protein interactions (Rose *et al.*, 1985; Chalmers and Marshall, 1995) (and references contained therein). In addition reverse turns are important structures of peptide hormones and other biologically active peptides and cyclic peptides.(Giannis and Kolter, 1993; Olson *et al.*, 1993; Kessler *et al.*, 1995)

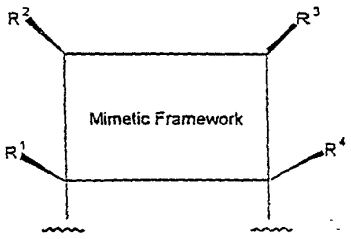
Peptide mimetics and peptide turn mimetics have as their object the replacement of a peptide sequence (a peptide turn) with a new compound which retains the elements essential for biological activity, thereby enabling or facilitating the development of novel pharmaceuticals devoid of the inherent problems of peptides - namely flexibility and poor pharmacodynamics. The essential elements for biological activity are thought to be the peptide sidechain groups (Farmer and Ariëns, 1982: Ball and Alewood, 1990), therefore a peptide mimetic should include the side chain groups to have the best chance of retaining biological activity. A peptide mimetic may then take the form of a framework for displaying sidechain groups in an appropriate arrangement.

The majority of reverse turns are beta turns. The generally accepted definition of the beta turn is a sequence of four residues where the distance between the alpha carbons of residue (i) and residue (i+3)

(defined as d) is less than 7Å, and the central residues (i+1, i+2) are non-helical.(Lewis *et al.*, 1973) The general structure is shown below and includes the phi (ϕ) and psi (ψ) backbone dihedral angles that are used to describe the conformation of the peptide backbone. A schematic conversion of the beta turn to a beta turn mimetic is also shown - the peptide backbone is here replaced by an undefined framework.

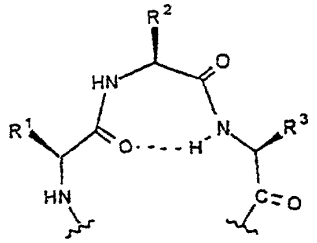


General structure of a hydrogen bonded β-turn. The four backbone dihedral angles traditionally used in turn classification are indicated, and also the position of the 7Å upper distance cutoff for d used for the definition of β-turns.



A schematic representation of a beta turn mimetic - the peptide backbone has been replaced by an alternative chemical framework, represented here by a rectangle

The gamma turn is generally defined by the presence of a hydrogen bond between C=O (i) and N-H (i+2) to form a pseudo seven membered ring as illustrated below (Milner-White, 1988). Where the equivalent hydrogen bond is present in a beta turn a pseudo ten membered ring is formed.



General structure of a γ-turn, defined by the presence of a hydrogen bond between the C=O of the (i) residue and the N-H of the (i+2) residue, as indicated.

The chemical synthesis of a framework having four independent chiral groups each with a wide range of possible functionality (for example, a beta turn mimetic) is a very significant synthetic challenge (Nakanishi and Kahn, 1996) as illustrated by the the fact that most proposed beta turn mimetics either do not provide for the incorporation of any sidechain functionality, or provide for a limited range of functionality, and at a limited number of positions. Reference may be made to reviews by Ball and by Hölzemann for illustration of these points (Ball and Alewood, 1990; Hölzemann, 1991; Hölzemann, 1991). In the case of mimetics that do provide for the incorporation of sidechain functionality, the syntheses are often complex and lengthy, and most seriously may require a different synthetic method for different sidechain sequences (i.e. the synthetic method is not generic). For example, in the work of Callahan, Huffman and Newlander on gamma turn mimetics the synthetic method varied depending on the sidechain sequence required - a 10 step sequence for a Gly-Phe-Leu mimetic, 13 steps for Phe-Gly-Val and 21 steps for Ala-Phe-Ala (Huffman *et al.*, 1988; Callahan *et al.*, 1992; Newlander *et al.*,1993). Given that the possible combinations of three residue sequences of the 20 natural amino acids is 8000 (20x20x20), and 160,000 for the four residue beta turn sequence, such non-generic methods are of limited use. The methods of Callahan and Huffman were further hampered by a lack of chiral control, as are most methods in the art.

In the development of peptide turn mimetics a further important issue is the reproduction of the variety of different turn conformations, particularly of the beta turn. Several different methods of describing turn conformation have been proposed, the traditional method having several turn types based on the backbone dihedral angles of the (i+1) and (i+2) residues i.e. I, I', II, II', III, III', IV, V, VIa, VIb, VII and VIII, with even this diversity of types being insufficient to adequately describe turn conformations.(Richardson, 1981; Wilmont and Thornton, 1990; Ball

et al., 1993) No *single* mimetic framework can accurately mimic this diversity of turns; a selection of mimetic frameworks is required.

The problems encountered in the development of peptide turn mimetic syntheses are discussed in a review by Kahn (Kahn, 1993) and reference may also be made to a review article entitled "Design of Peptidomimetics" (Nakanishi and Kahn, 1996) which discusses aspects of mimetic design and developments regarding peptide mimetics.

The uses of reverse turn mimetics (and peptides or other compounds containing reverse turn mimetics) in drug development have been described in the art, notably in publications by Kahn and co-workers (Kahn, 1996; Nakanishi and Kahn, 1996; Qabar *et al.*,1996) and references contained therein. An important example of the application of reverse turn mimetics is the production of mimetics of known biologically active cyclic peptides (typically penta- or hexapeptides), as illustrated by Hirschmann and co-workers with □-D-glucose based mimetics.(Hirschmann *et al.*,1992; Hirschmann *et al.*, 1993)

Other beta turn mimetics having biological activity are known in the art. For example, U.S. Patent 4535169 discloses a method for the synthesis of beta turn mimetics which can incorporate a functional substitution for the (i+3) sidechain (only), and Krystenansky *et al.* disclose a leucine enkephalin mimetic based on this method which had analgesic activity one third the potency of morphine (Krstenansky *et al.*, 1982).

Reference may also be made to U.S. Patents 5475085 and 5618914 and International Publication WO96/22304 (all Kahn, M) which describe methods for the synthesis of a range of reverse turn mimetics. These mimetics are all produced by a modular synthesis technique (that may be applied to solid phase synthesis) which involves amino acid derivatives and various dipeptide azetidinones synthesised by a variety of techniques. An important common step in all of the syntheses of these mimetics is the cyclisation reaction which involves the azetidinone as activated ester component. Conformational variation is introduced to these mimetics by the inclusion of a variable component ("X") in the ring

of the cyclic turn mimetics. It should be noted that with two exceptions (the parent mimetics which have X=NH and have a ten or eleven membered ring) the beta turn mimetics produced by these methods have ring sizes of twelve members and above. Such large rings allow many conformations with d>7Å, the mimetic conformations are therefore biased away from the accepted definition of a beta turn (d less than 7Å), or more importantly the conformations are biased away from the most common reverse turn conformations which have d in the range of 4.5Å to 6Å (Rose *et al.*, 1985; Gardner *et al.*,1993). Enkephalin mimetics have been made (Gardner *et al.*, 1993) and also mimetics of a loop of CD4 that inhibit binding of HIV gp120 and infection of human lymphocytes (Chen *et al.*, 1992). The synthetic methods described for the majority of these mimetics appear to be limited with respect to the possible functionality at the (i) and (i+1) positions, and indeed no mimetic with any functionality at the (i+1) position (other than -H = glycine = no sidechain) appears to have been described at this time.

Reference may also be made to International Publication WO97/15577 (Kahn, M) which describes the synthesis of bicyclic reverse turn mimetics and chemical libraries containing such reverse turn mimetics. While concise, the synthetic methods do not provide for control of chirality at all positions, and the degree of sidechain function generality is questionable at two of the four positions. Furthermore the structure of the mimetics means they are not able to be easily incorporated in a peptide sequence, nor do they reproduce the relative positioning of the sidechain groups in the ideal manner (each sidechain attachment position should ideally be separated by three covalent bonds, as in a peptide).

Reference may also be made to the turn mimetics of Virgilio *et al.* (Valle *et al.*, 1989; Virgilio and Ellman, 1994; Virgilio *et al.*, 1996) that incorporate functionality at the (i+1), (i+2) and (i+3) positions (but not the (i) position), and that do not allow for incorporation of the mimetic in a peptide sequence (i.e. no amino and carboxy terminal groups in addition to the sidechains are present).

Reference may be made to U.S. Patents 5438188 and 5470849 (Callahan and Huffman) that describe biologically active compounds containing gamma turn mimetics, providing further illustration of the general utility of reverse turn mimetics.

Reference may also be made to International Publication WO95/25120 that describes the use of turn mimetics in the synthesis of peptide vaccines for generating a protective immune response in warm blooded animals.

In the methods and mimetics of the aforementioned references several common problems are evident: limited numbers of sidechains are able to be reproduced, there is limited control of chirality in the syntheses and a limited range of sidechain functions could be included. In addition, many of the syntheses of turn mimetics described are relatively long and complex, even when not all the sidechain functions are included, for example the syntheses of certain enkephalin mimetics were in the range of approximately 15 to 21 steps (Gardner *et al.*, 1993). There is therefore still a need in the art for peptide mimetics that can incorporate a wide range of sidechain functions in all positions, that can be readily synthesised with control of chirality, and that have a wide range of conformations corresponding to those found in native peptides.

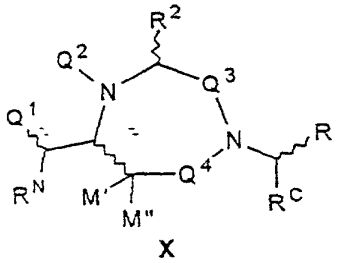
OBJECT OF THE INVENTION

It is the object of the invention to provide novel compounds useful as, and useful for the synthesis of, conformationally constrained mimetics of biologically active peptides and proteins (peptide mimetics). In particular, the invention provides new compounds and methods for the synthesis of new peptide reverse turn mimetics that can display a wide range of sidechain functions at all sidechain positions, can be incorporated in a peptide sequence, can be readily synthesised, and have a variety of conformations.

SUMMARY OF THE INVENTION

This invention describes novel compounds useful for the synthesis of peptide mirnetics, and describes the use of these compounds

for the synthesis of novel reverse turn mimetics. The reverse turn mimetics of the invention have the general structure **X**, or in a preferred embodiment the general structures **I-VI** (which are subsets of the general structure **X**; see below and Figures 1 and 2 on the attached sheets; the structures are fully described in the detailed description following this summary).



X

It has now been discovered that B-allyldialkylboranes (e.g. **Rg1a-i**, Figure 3) react with imines 3 (Scheme 1) to give the novel allyl amines **4a-d** in good yield and with a very high degree of chemo- and stereoselectivity. This is surprising because in contrast to these good results, allylation with the related B-allyldialkoxyboranes (e.g. **Rg1j**, Figure 3) or allylcopper or allylzinc reagents gave inferior results with racemisation and reaction at other functional groups. The reaction of imines **3** to form compounds **4a-d** and formation of the related compounds **5-8a-d** (all of which are made from compounds **4a-d**) forms the basis of the synthesis of all the compounds of the invention, and hence the invention. Thus the allyl amines **4a-d** are suprisingly valuable intermediates for the synthesis of new peptide mimetics, particularly reverse turn mimetics, enabling the synthesis of the significant variety of new reverse turn mimetics of the invention (having the general structure **X**), by the variety of different pathways described herein. All the mimetic systems of the invention can be incorporated into peptide sequences (i.e. they include amino and carboxy termini in addition to the sidechain

functions), or if desired the amino and/or carboxy termini can be omitted from the mimetic.

As described above, there is a need for a wide range of different mimetics to better reproduce the wide range of conformations found in native reverse turns. The turn mimetics of the invention have a large variety of novel functionalised ring structures, each of these therefore having novel conformational characteristics. Furthermore, the structure and ring sizes of many of the turn mimetics make them well suited to the reproduction of the geometry of the more common native reverse turn conformations (those having d of 4.5Å to 6Å).

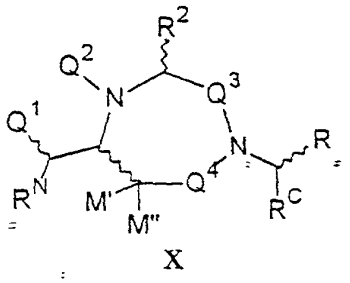
The synthetic methods described in this invention are generally superior to the prior art in terms of the capacity to include a wide range of side chain functions, in all the sidechain positions, without significant changes in the synthetic method; that is, the methods are more truly *generic*. In addition, the control of chirality in the synthesis of the mimetics of the invention is superior to the prior art - an important consideration in the elucidation of structure-activity relationships and the development of novel pharmaceuticals, and other commercially useful peptide mimetics, as diastereomeric mixtures are normally unsuitable and may be impractical or impossible to separate on a commercial basis. Furthermore, selective access to a range of different diastereomers for a particular mimetic with a given sequence provides a selection of different conformations. Thus in a mimetic with four chiral centres there are a total of 16 (2^4) possible diastereomers - each having a different conformation. The methods of the invention allow for a high level of chiral control by using available chiral starting materials, non-racemising conditions and diastereoselective reactions.

The invention includes all novel intermediates used in the preparation of the turn mimetics and more generally useful for the preparation of peptide mimetics, particularly **4-8(a-d)**, Scheme 1 and **10**, Scheme 2. Also **11-12**, Scheme 3; **13-14**, Scheme 4; **16-17**, Scheme 5; **18-19**, Scheme 6; **21-22**, Scheme 7; **23(a-d)-25(a-d)**, **26**, Scheme 8; **27-**

28, Scheme 11; **29-34**, Scheme 12; **35(a-c)**, **36-38**, Scheme 13; **43-46**, Scheme 15.

DETAILED DESCRIPTION OF THE INVENTION

The peptide mimetics of this invention have the general structure **X**, shown below and defined as follows:-



X

wherein R and R^2 and other R groups referred to hereinafter inclusive of R^1, R^3, R^4, R^{n+3} and R^{n+4} etc. unless otherwise indicated, are amino acid side chain groups, each independently chosen and therefore the same or different (two separate R groups in the same mimetic do not require a different suffix to indicate that they are independently chosen and can be the same or different). The definition of "amino acid side chain group" as used in this document is the same as the definition of "amino acid side chain moiety or derivative" as described in International Publication WO97/15577, pages 7-9 (Kahn, M), incorporated herein by reference. Amino acid side chain groups typically correspond to, but are not limited to, those found in natural amino acids and derivatives and in common unnatural amino acids. Thus for glycine R = hydrogen; for alanine R = methyl; for phenylalanine R = $-CH_2Ph$; for homophenylalanine R = $-CH_2CH_2Ph$; for valine R = $-CH(CH_3)_2$; for leucine R = $-CH_2CH(CH_3)_2$; p-nitrophenylalanine R = $-CH_2((4\text{-}NO_2)Ph)$; naphthylalanine R = $-CH_2$-naphthyl etc. Also included are cyclic amino acid sidechains such as for proline, hydroxyproline and homoproline which involve a cyclization to the adjcent backbone nitrogen atom or the equivalent position, but only where this is possible (i.e. the amine or

equivalent atom is not already substituted as part of the heterocyclic mimetic framework).

Z is normally hydrogen, methyl, ethyl, formyl or acetyl, and may alternatively be R or $-CH_2R$ or -C(O)R where R is an amino acid side chain group, or alternatively Z is part of a cyclic amino acid side chain group joined to R^2 (for example to mimic a proline residue at position (i+1)). For **II(i)** referred to hereinafter, Z cannot be hydrogen due to compound instability.

R^C is the carboxy terminal part of the mimetic, typically $-C(O)Pg^C$ or alternatively hydrogen or an amino acid side chain group R or $-CH_2R$.

Pg^C (and $Pg^{C'}$ etc.) is a protecting group for carboxylic acid, typically including, but not limited to: alkoxy, benzyloxy, allyloxy, fluorenyl methyloxy, amines forming easily removable amides, or alternatively an appropriate cleavable linker to a solid phase support, or such a support itself, or alternatively hydroxy –OR, -NHR or remaining C-terminal portion of the mimetic system as described below.

R^N is the amino terminal part of the mimetic, i.e. $-N(Z')Pg^N$,

Z' is normally hydrogen, alternatively methyl (to mimic an N-methyl amino acid residue at position (i)), or alternatively part of a cyclic amino acid side chain group joined to R^1 (for example, to mimic a proline residue at position (i)).

Pg^N (and $Pg^{N'}$) is a protecting group for amine, typically including, but not limited to: Boc, Cbz, Fmoc, Alloc, trityl; or alternatively an appropriate cleavable linker to a solid phase support, or such a support itself, or alternatively hydrogen or R or -C(O)R where R is an amino acid side chain group, or alternatively part or all of the remaining N-terminal portion of the mimetic system, as described below.

M', M" are normally hydrogen, alternatively one or more may be C_1-C_4 alkyl (preferred methyl), chloro, C_1-C_4 alkoxy (preferred methoxy).

$Q^1 = R^1$ and $Q^2 = Z$; alternatively there is a cyclisation from Q^1 to Q^2 and then in preferred embodiments of the invention Q^1Q^2 = CH(R)C(O) or $-CH_2CH(R)C(O)-$ or $-CH_2CH_2CH(R)C(O)-$. Q^1Q^2 can also be: $-CH(R)CH_2-$ or $-CH_2CH(R)CH_2-$ or $-CH_2CH_2CH(R)CH_2-$ or $-CH_2CH(R)-$ or $-CH_2CH_2CH(R)-$ or $-CH(R)CH_2CH_2-$ or $-CH_2CH(R)CH_2CH_2-$ or $-CH(R)CH_2C(O)-$ or $-CH_2CH(R)CH_2C(O)-$.

Q^5 = hydrogen, C_1-C_4 alkyl, chloro or C_1-C_4 alkoxy and Q^3 = Y or $-C(O)NHCH(R)Y-$ or $-C(O)ENHCH(R)Y-$; or alternatively when $Q^3 = -C(O)N(Q^5)CH(R)Y-$ Q^5 is a covalent bond from the Q^4 group to the nitrogen atom in Q^3 (a cyclisation forming a bicyclic ring system).

Y is selected from the group consisting of C(O) and CH_2 and Q^4 is selected from the group consisting of CHM^l, C(O), $CH(Q^5)CH_2$ and $CH(Q^5)C(O)$ with the provisos that:

(i) $Q^4 = CH(M^l)$, Y is C(O);

(ii) Q^4 = C(O), Y is CH_2;

(iii) $Q^4 = CH(Q^5)CH_2$, Y is C(O); and

(iv) $Q^4 = CH(Q^5)C(O)$, Y is CH_2.

$E=-(AA)_n-$ where n = 1, 2, 3, 4... (n = 1 to about 300, but more typically n is between 1 and 30) and AA is an amino acid residue (e.g. AA = $-NHCH(CH_3)C(O)-$ for alanine); E is therefore a loop of n amino acids which are linked in a cycle by the rest of the mimetic system. The loop may also incorporate non-alpha amino acids, alpha dialkyl amino acids or any other amino acid which confers favourable properties on the mimetic system, for example increased binding affinity, or ease of detection, identification or purification. The invention, when used with such larger loops, is functioning as a covalent hydrogen bond mimic (another aspect of the invention), as generally described by Arrhenius *et al.* (Arrhenius *et al.*, 1987) and also in U.S. Patent 5807979 (Arrhenius *et al.*).

Preferred embodiments of the invention are the structures I-VI, as illustrated in Figures 1 and 2 and defined in Table 1:-

Table 1

Mimetic	Q^1	Q^2	Q^3	Q^5
I	R^1	Z	Y	-
II	R^1	Z	-C(O)NHCH(R)Y-	M^l
III	R^1	Z	-C(O)NHCH(R)C(O)-NHCH(R)Y-	M^l
IV	R^1	Z	$-C(O)N(Q^5)CH(R)Y-$	Q^3
V	$-CH(R)C(O)Q^2$	Q^1	Y	M^l
VI	$-CH_2CH(R)C(O)Q^2$	Q^1	Y	M^l

Recursive entries of Q groups in Table 2 indicate a cyclisation - thus mimetics V and VI have a cyclisation between Q^1 and Q^2, and mimetic IV has a cyclisation between Q^3 and Q^5. In the Tables, the groups Q^1-Q^5 and Y are as defined above, and the other groups are asdefined herein.

The compounds of this invention have been designed to allow for incorporation in a peptide or protein chain, or for covalent attachment to any molecule or group that may be useful for the enhancement of the biological activity, or other property, of the peptide mimetic. Thus the mimetics typically contain amino and carboxy termini independent of the sidechain functions. The term "remaining C- (or N-)

terminal portion of the mimetic" is any group, molecule, linker, support, peptide, protein, nucleoside, glycoside or combination of these, covalently linked to the mimetic. Typically such remaining portions would be peptides or combinations of peptides and other mimetics, or compounds to facilitate detection or identification, or to improve the pharmacodynamics or other useful feature of the mimetic system.

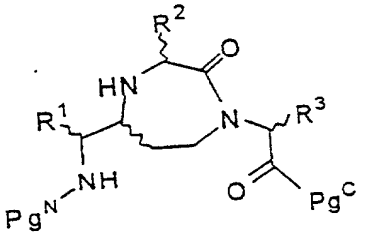
In addition, any R group (an amino acid side chain group) may serve as an attachment point to a solid support, or to a linker to a solid support, or as a covalent attachment point for another molecule that may be useful for the enhancement of the biological activity, or other property, of the mimetic, as described above for the remaining C- or N-terminal portions of the mimetic.

The term "cleavable linker" and "solid phase support" are as defined in International Publication WO97/1557

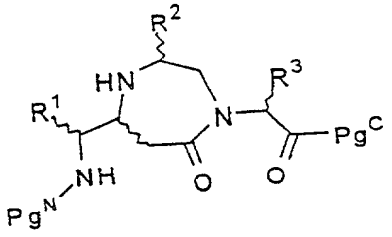
The use of a wavy line for one of the bonds at a chiral centre in the general structures **X** and **I-VI** and in the other structures in the Figures and Schemes indicates that the centre may be in either the (R) or (S) configuration, or be a mixture in any proportion of the (R) and (S) configurations. In most circumstances it is preferable to avoid mixtures of configurations unless the intention is to provide a mixture of diastereomers for example for the purpose of more efficient screening (by the use of a mixture) or for synthetic expediency. Chirality at the amino acid side chain positions in the compounds of the invention (e.g. at R^1 to R^4) is controlled by the use of chiral starting materials (L or D amino acids) and the avoidance of synthetic conditions which cause racemisation. The configuration at chiral centres formed in the mimetic synthesis is dependent on several factors and can be controlled in several cases, but in other cases mixtures of diastereomers will result, which can potentially be separated by physical means. A significant advantage of the invention is the superior level of chiral control possible at the chiral centres in the mimetics.

EXAMPLES OF PREFERRED EMBODIMENTS OF THE MIMETICS

□-Turn mimetics **I(i)a**, **I(ii)a** (M, M', M'', Z and Z' = hydrogen):

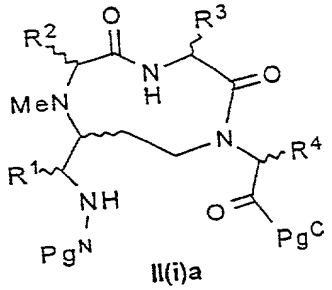


I(i)a

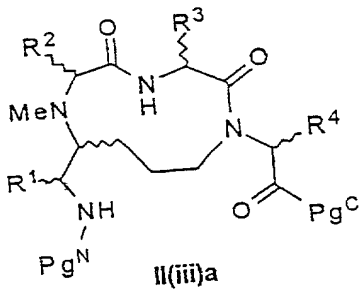


I(ii)a

□-Turn mimetics **II(i)a**, **II(iii)a** (M, M', M'' and Z' = hydrogen, Z = Me):

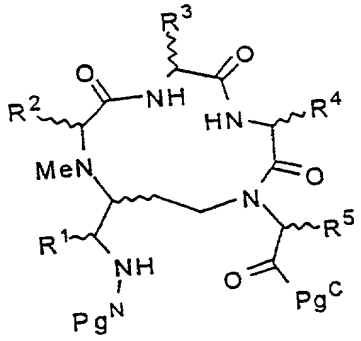


II(i)a

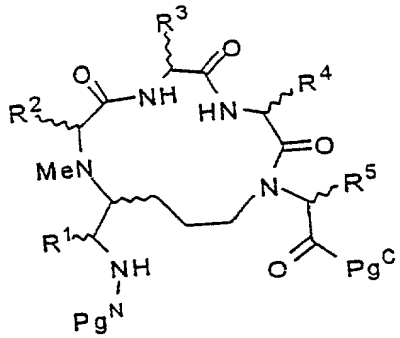


II(iii)a

□-Bulge mimetics **III(i)a**, **III(iii)a** (M, M', M'' and Z' = hydrogen, Z = Me):

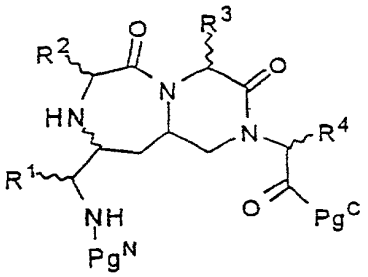


III(i)a

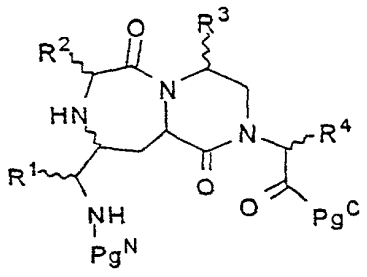


III(iii)a

Bicyclic □-turn mimetics **IV(i)a**, **IV(ii)a** (M, M', M'', Z and Z' = hydrogen):

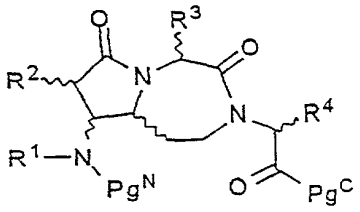


IV(i)a

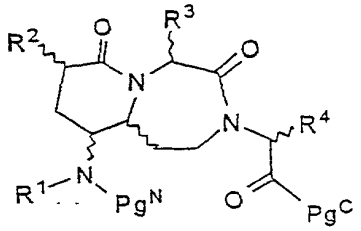


IV(ii)a

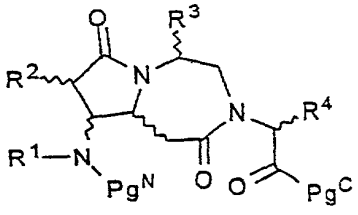
Bicyclic □-turn mimetics **V(i)a**, **VI(i)a**, **V(ii)a**, **VI(ii)a** (M, M'and M'' = hydrogen)



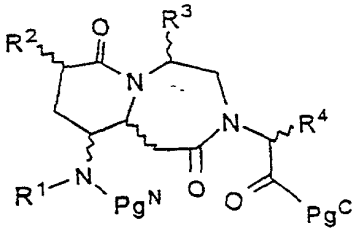
V(i)a



VI(i)a



V(ii)a

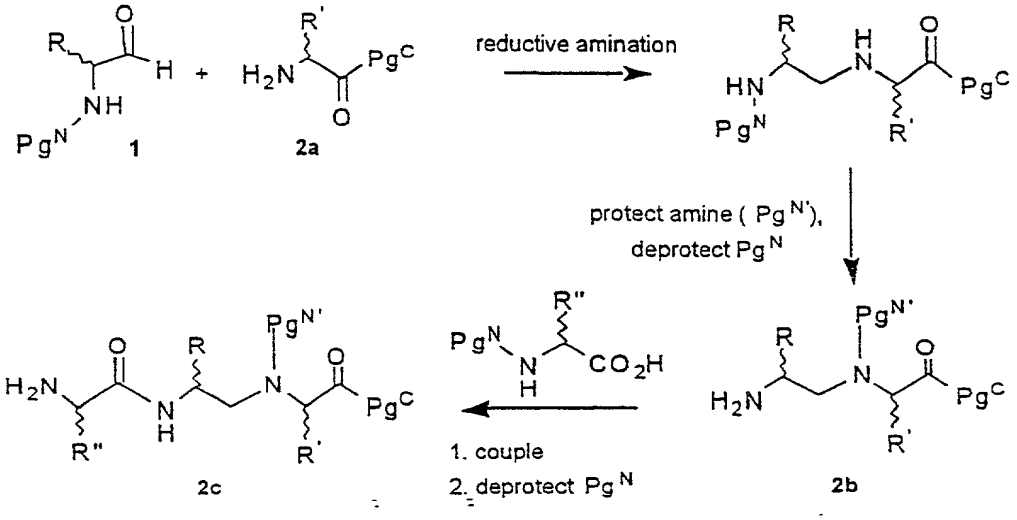


VI(ii)a

The synthesis of all the mimetics described in this specification may proceed initially by the same general synthetic procedure for formation of the common intermediates - reaction of imines **3** with allyl metal reagents **Rg1** (allyl boranes preferred) to give the allyl diamines **4**, which are new, as described in Scheme 1. The other compounds of Scheme 1 (i.e. **5-8**) may all be derived from the allyl diamines **4**, as described in Scheme 1 and in the comments below. The

allylation reaction of imines **3**, which falls within the scope of the invention, is remarkable for its mildness and selectivity - allowing a wide range of functional groups to be present in the rest of the molecule, a very important consideration in the synthesis of peptide mimetics. Another important feature of the reaction of allylboranes with the imines **3** is that it proceeds in good yield (e.g. >50% isolated yield) in the sterically hindered general case where R^1 and R^2 are both not hydrogen - i.e. for all mimetics of dipeptides not containing glycine. Scheme 1 and all subsequent Schemes describe the preferred case of R^N=NHPg^N and R^C=C(O)Pg^C (Figures 1 and 2), analogous methods apply in the general case.

In relation to Scheme 1, preparation of the imines **3** is completed by condensation of an amino acid aldehyde (compound **1**) with an amine (**2a-d**). The aldehydes **1** may be prepared by either oxidative procedures from the corresponding N-protected amino alcohol, or reduction of an N-protected amino acid derivative (Fehrentz and Castro, 1983), the different approaches have been reviewed, (Jurczak and Golebiowski, 1989) (see also Goel *et al.*, 1988, *Org. Syn.* **67** 69). The amines **2a** are amino acid esters (or other acid protected amino acid derivatives), which are commercially available or may be synthesised by standard procedures from amino acids. Amines **2b-2d** are prepared by reductive amination of an amine **2a** and an amino acid aldehyde **1**:



Amines **2d** are prepared by repeated coupling/deprotection steps (as in conversion of **2b** to **2c**), standard techniques of peptide synthesis.

The reductive amination procedure for the alkylation of amines by aldehydes is well established in the art. (See for example, Sasaki and Coy, 1987, Peptides **8** 119), the preferred reagents are sodium cyanoborohydride (Borch *et al.*, 1971; Hutchins and Natale, 1979; Gribble and Nutatits, 1985), or more preferred sodium triacetoxyborohydride in dichloroethane. (Abdel-Magid *et al.*, 1996).

Methods for the formation of amide bonds (coupling) are well established in the art. For coupling at more hindered amines the use of certain reagents, for example those based on 1-hydroxy-7-azabenzotriazole (Ehrlich *et al.*, 1993; Carpino *et al.*, 1994), or the use of amino acid fluorides (Carpino *et al.*, 1990; Wenschuh *et al.*, 1994) is advantageous.

Protecting strategies for the synthesis of peptides and peptide mimetics are well established in the art, for example a five dimensional orthogonal strategy was used by Hirschmann and co-workers in the synthesis of a somatostatin mimetic.(Hirschmann *et al.*, 1996) A more general reference work on protection/deprotection is the monograph by Greene and Wuts.(Greene and Wuts, 1991).

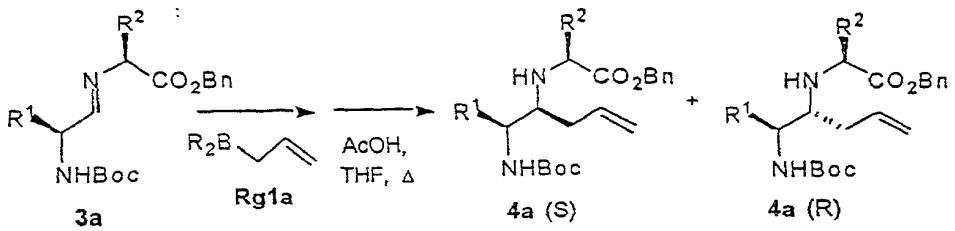
The example syntheses described in this document use solution phase chemistry. The mimetics may also be synthesised by analogous solid phase techniques, or by a combination of solid phase and solution phase techniques, or the mimetics may be incorporated in normal solid phase peptide synthesis in the same way as a standard protected amino acid derivative. A review by Früchtel and Jung (Früchtel and Jung, 1996) details the state of the art in solid phase organic synthesis (in 1996).

It will be clear to those skilled in the art that the mimetics of the invention, due to their generic methods of synthesis, are suited to the application combinatorial chemistry techniques (more specifically combinatorial organic synthesis) and certain associated identification and screening techniques. The application of combinatorial and associated technologies to drug discovery are well known in the art and have been reviewed, see for example papers by Gallop *et al.* and by Gordon *et al.*, and references therein, incorporated herein by reference (Gallop *et al.*, 1994; Gordon *et al.*, 1994). Additionally, reference may be made to a review by Thompson and Ellman on the synthesis and application of small molecule libraries, and references therein, incorporated herein by reference.(Thompson and Ellman, 1996).

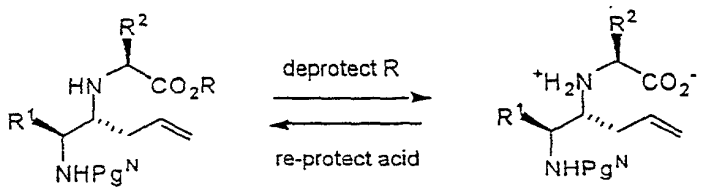
The imines **3** form rapidly at room temperature on mixing of the amine and aldehyde in an appropriate solvent, e.g. CH_2Cl_2 or diethyl ether, with liberation of water. The water is removed with a drying agent, e.g. dried $MgSO_4$, which is subsequently removed by filtration. The imines are then reacted with an allyl metal reagent (**Rg1**) to give, after work-up, compounds **4** (Scheme 1).

In relation to reagents **Rg1**: standard allyl organometals, such as allyl magnesium bromide, are unsuitable for reaction with imines **3** due to a lack of selectivity for the imine function over the carboxylic acid derived groups (esters, amides) also present in **3**. Allyl copper and zinc reagents have been used in selective reactions with imines (Bocoum *et al.*, 1991; Basile *et al.*, 1994) but in the case of imines **3** these reagents

result in extensive racemisation at the □-imine chiral centre, and attack esters present in the imine to a significant extent. While some of the desired target **4** may be produced by many allyl metal reagents on reaction with **3**, the reaction product typically contains a mixture of four diastereomers and also by-products from reaction at the carboxylic acid derived groups (especially esters). In contrast to these results, reaction of the imines **3** with allyl boranes, such as B-allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN), **Rg1a**, gives excellent results and reasonable diastereoselectivity (>50% isolated yield based on crude aldehyde, and ~80:20 diastereoselectivity where R^1 is not H).



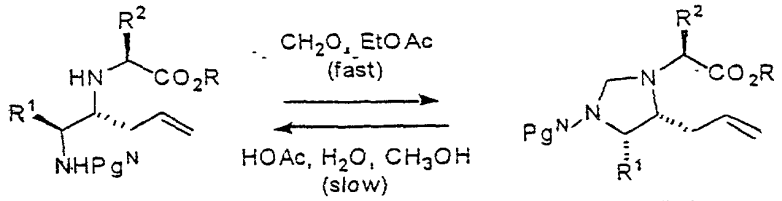
By the use of allyl trialkylboranes with appropriate chiral alkyl groups such as B-allyl-diisopinocampheylborane (allyl-DIP, **Rg1b** and **Rg1c**), or the diisocaranylboranes **Rg1d-e** it is possible to produce give only the major product (one diastereomer, >99:1) in good yield and purity. The configuration at the new stereocentre was determined to be (R) when using aldehyde derived from natural (S) configuration amino acids, and the stereocontrol exerted by the □-aldehyde chiral centre was dominant over the effect of chiral boron ligands and over the effect of the other amino acid chirality in all cases examined. The (+)DIP reagent **Rg1b** gave higher diastereoselectivity on imines derived from natural (S) configuration aldehydes than **Rg1c** (from (-)DIP). The purity of the allylation products **4a** may also be improved by the removal of the ester protecting group Pg^C to give a crystalline amino acid which can be recrystallised (e.g. from ethanol/water) to the desired level of purity and then reprotected.



4a (R) **4a** (R), Pg ^{C}=H crystalline derivative

The use of crotyl (**Rg1f**, **Rg1h-i**), methallyl (**Rg1g**) or other substituted allyl derivatives leads to bridge substituted mimetics (mimetics where at least one of M, M' and M" is not hydrogen) with further opportunities for stereocontrol. The less reactive allyl boronate allyldimethoxyboron (**Rg1j**) was found to give inferior results (significant epimerisation at C□(i)) compared to the allyltrialkylboranes. Many allylboronate and related reagents (e.g. **Rg1k-m**) are described in the literature, and some of these may be more effective than allyldimethoxyboron for the conversion of **3** to **4**. Selective reactions using allylic metals have been reviewed by Yamamoto and Asao, Tables IV and V in the review (pp 2224-2230) list a wide variety of allyl boron reagents.(Yamamoto and Asao, 1993) The preparation of allyl-9-BBN and other allyltrialkylboranes has been described by Brown and coworkers (Kramer and Brown, 1977; Brown and Jadhav, 1983; Brown and Jadhav, 1984; Brown and Bhat, 1986; Brown, Randad *et al.*, 1990) Allyltrialkylboranes may also be prepared by the reaction of the corresponding B-chloro or B-methoxy derivative with an allylmagnesium bromide (-78_C, diethyl ether), and reacted in situ with the imine (Yamamoto and Asao, 1993). The imines **3** formed from two non-glycine derivatives (i.e. R^1 and R^2 not H) are significantly hindered about the imine nitrogen, and the use of bulky boron ligands (such as diisopinocampheyl) can reduce the reaction yield. For high yield and selectivity smaller chiral B-allyl compounds, e.g. those based on 2,5-dimethylboracyclopentane are preferred (e.g. **Rg1n**, Figure 3).

In relation to protection and deprotection of compounds **4** and **5**: addition of formaldehyde solution to **4** results in the rapid formation of imidazolidines **5**; the relative configuration in the major allylation products **4** results in a 4,5-cis-substituted imidazolidine **5**. This protection strategy is important for further reaction of these compounds. The protecting group is removed by treatment with aqueous acid (e.g. aqueous methanolic acetic acid).

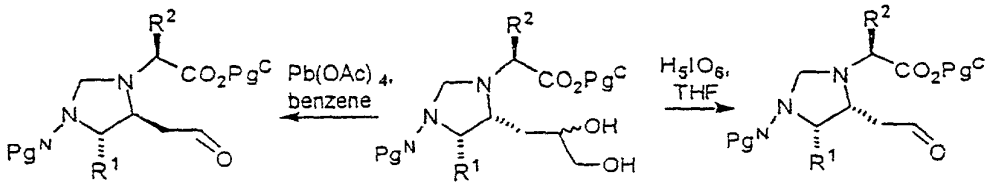


4a (R) **5a** 4,5-cis

A similar protection system is the dibenzyltriazone group of Knapp and co-workers,(Knapp *et al.*, 1992) the paper describes other deprotection conditions and is incorporated herein by reference. An alternative deprotection method involves the hydrogenation of the imidazolidine system to an amine N-methyl group (40psi H_2, Pd-C, MeOH, 48hrs), a conversion that can be used to give mimetics where Z = Me.

In relation to oxidation of alkenes **5**: acids **6** can be synthesised directly by oxidative cleavage of the alkenes **5**, e.g. by $RuCl_3/NaIO_4$; aldehydes/ketones **8** may be synthesised directly from **5** by ozonolysis (for oxidation methods see for example the monograph by Hudlicky (Hudlicky) and references therein), but this process is not sufficiently selective and results in over-oxidation and the formation of other by-products. Preferred is the two step process of dihydroxylation (OsO_4, N-methylmorpholine-N-oxide (NMO),*t*BuOH/water) (VanRheenen *et al.*, 1976; Ray and Matteson, 1980) to **7** followed by oxidative cleavage ($Pb(OAc)_4$ in benzene or H_5IO_6 in THF).(Hudlicky, 1990) Examination of the products of the oxidation reactions led to the surprising discovery that cleavage with $Pb(OAc)_4$ resulted in isomerised product with the 4,5-substituents now trans, not cis as in the starting material. It was further

discovered that oxidation of the diol with H_5IO_6 in dry THF resulted in retention of the 4,5-cis configuration in the aldehyde product **8**. The cis aldehydes can also be isomerised to the trans by treatment with catalytic acid, e.g. HCl in $CHCl_3$.



8a 4,5-trans, inversion

7a 4,5-cis

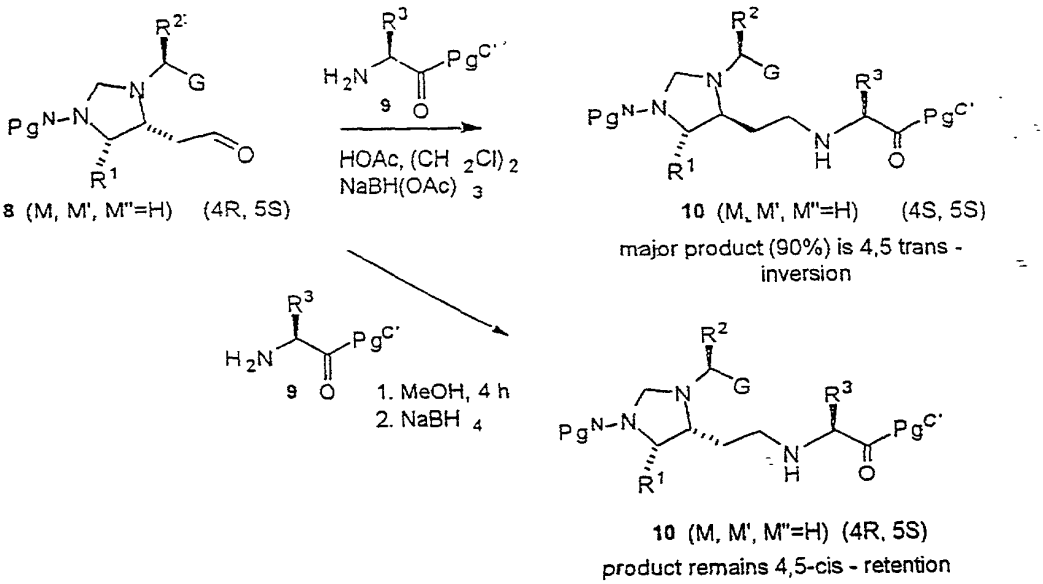
8a 4,5-cis, retention

These important discoveries now allow selective access to all of the eight possible diastereomers of the aldehydes **8** and the acids **6**, and therefore control of the majority of the chirality in all the mimetic systems described in the invention.

In relation to the oxidation of aldehydes **8** to acids **6**: many oxidation reagents may effect this conversion, e.g. pyridinium dichromate.(Hudlicky, 1990) Glycols **7** may also be oxidised directly to acids, e.g. by $RuCl_3/NaIO_4$. In relation to reduction of acids **6** to aldehydes **8**: carboxylic acids **6** can be converted to aldehydes by the same general methods used for the formation of protected □-amino aldehydes described above.(Jurczak and Golebiowski, 1989). The carboxylic acid can be selectively reduced to the alcohol in the presence of carboxylic esters by the use of borane (Brown and Krishnamurthy, 1979), then oxidised to the aldehyde as previously described.(Jurczak and Golebiowski, 1989)

In relation to **Scheme 2**: Aldehydes/ketones **8** undergo reductive amination with amino esters **9** by the methods previously described. The preferred method is $NaBH(OAc)_3$ in dichloroethane (room temperature). Surprisingly, it was discovered that the reductive amination of 4,5-cis imidazolidine aldehydes **8** resulted in the formation of the 4,5-

trans amines **10** (~9:1 trans:cis). This isomerisation reaction is rapid (much faster than that of aldehydes **8**) as the reductive amination reaction is complete in only a few minutes. It was further discovered that the isomerisation reaction could be prevented by the pre-formation of the imine between the aldehyde **8** and amine **9** (in MeOH, 2-4 h at room temperature) with rigorous exclusion of acid, followed by reduction with sodium borohydride to give the cis amine **10** from the cis aldehyde. This discovery allows the selective synthesis of either the 4,5-cis diastereomer or 4,5-trans (9:1 with cis) diastereomer of the amines **10** starting from the 4,5-cis aldehyde **8**.



8 (M, M', M"=H) (4R, 5S)

10 (M, M', M"=H) (4S, 5S)
major product (90%) is 4,5 trans - inversion

10 (M, M', M"=H) (4R, 5S)
product remains 4,5-cis - retention

It is important to appreciate that the methods described above allow the selective synthesis of all sixteen relative and absolute diastereomers of compounds **8** and **6**, and all thirty two diastereomers of compounds **10**. The ability to selectively synthesise these diastereomers is a significant advantage of the invention.

In relation to **Scheme 3**: Deprotection of **10** is by standard methods consistent with the overall protecting strategy, as previously discussed. Many coupling agents are suitable for effecting the cyclisation

of **11** to **12**, typical conditions: THF, BOP or HBTU or HATU, EtN(*i*-Pr)$_2$ (DIEA). The imidazolidine group is then deprotected (as previously described) by hydrogenation (MeOH, H_2-Pd/C) when Z = Me, and by hydrolysis (H^+, H_2O) for Z = H (other Z groups may be introduced by acylation or alkylation of the deprotected secondary amine).

In relation to **Scheme 4**: Deprotection and cyclisation of **6b** to **13**, **14** and **I(ii)**: - standard deprotection and coupling (cyclisation) methods are used. Other conversions are as previously described.

In relation to **Scheme 5**: As previously discussed, coupling reactions to relatively hindered (usually secondary) amines often require the use of specialised coupling conditions such as acid fluorides **15**, as described by Carpino *et al.* (Carpino *et al.*, 1990; Wenschuh *et al.*, 1994) Protecting groups $Pg^{N'}$ and $Pg^{C'}$ (in **16**) are typically benzyloxycarbonyl (Cbz) and benzyl ester, simultaneously deprotected by hydrogenation (0.1M HCl in EtOH, H_2-Pd/C), cyclised using the BOP coupling reagent in THF or DMF, followed by conversion (deprotection) of the imidazolidine group to N-Me by hydrogenation as previously described.

In relation to **Scheme 6**: Standard deprotection/ coupling conditions as previously described.

In relation to **Scheme 7**: Where R^4 is a □-branched amino acid side chain (such as in Valine) then the coupling of **6a** and **20** may require the use of HATU or other system suitable for a hindered coupling when bulky sidechain groups are present, as previously discussed. Conditions and protecting groups for the conversion of **21** to **19** are the same as for the conversion of **16** to **II(i)**, Scheme 5.

In relation to **Scheme 8**: Hydroboration of alkenes is well known in the art, see for example monographs by Brown (Brown, 1975; Pelter *et al.*, 1988) The resulting alkyl boranes can be oxidised to alcohols (using alkaline hydrogen peroxide, or in a preferred embodiment using trimethylamine oxide, or other amine oxide, to form the borate with subsequent liberation of the alcohol by transesterification) (Soderquist and Najafi, 1986). Alternatively, treatment of the borane with acid

dichromate or, in a preferred embodiment, with pyridinium chlorochromate (PCC) gives the aldehyde (Brown *et al.*, 1980; Brown *et al.*, 1986). The aldehydes so formed may be reductively aminated on to amines **9** by the methods previously described.

In relation to **Schemes 9-11**: Standard synthetic techniques, previously described.

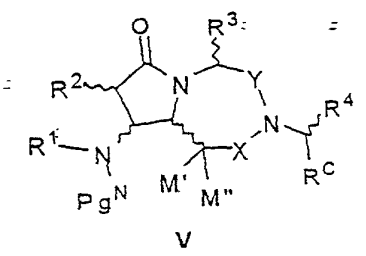
Methods for the synthesis of beta bulge (n=1, **III(i-iv)**) and higher loop mimetics (n>1), follow the corresponding methods for the synthesis of beta turn mimetics **II(i-iv)**. Appropriate protecting groups are chosen so that extra residues can be added to the system prior to cyclisation, as illustrated in Scheme 11 for the synthesis of a **III(i)** mimetic.

In relation to **Scheme 12**: Conversion of 1,2-diols **7** to epoxides **29** (dehydration) may be achieved with a number of reagents, for example triphenylphosphine and a dialkylazodicarboxylate (the Mitsunobu reagents) (Carlock and Mack, 1978; Robinson, Barry *et al.*, 1983) or TsCl/NaOH/$PhCH_2NEt_3^+$ Cl^-.(Szeja 1985). The epoxides **29** alkylate amines **9** on warming in ethanol or DMSO solution to give the amino alcohols **30**. The alcohol may then be oxidised to the ketone **32** by the use of TPAP (tetrapropylammonium perruthenate) with N-methylmorpholine-N-oxide in CH_2Cl_2/acetonitrile by the method of Griffith and Ley (Griffith and Ley ,1990). For **32** typically $Pg^{N'}$=Cbz and $Pg^{C'}$=O-benzyl, then by the use of catalytic hydrogenation conditions (EtOH, H_2-Pd/C) the protecting groups are both removed and intramolecular reductive amination of the free amine to the ketone occurs to give **33**. Coupling using the BOP reagent (or other suitable conditions) followed by deprotection of the imidazolidine group as previously described gives the bicyclic mimetic **IV(i)**. Alternative syntheses are possible with the use of mild oxidising reagents to convert the glycols to carbonyl compounds, followed by reductive amination (Frigerio and Sangostino, 1994).

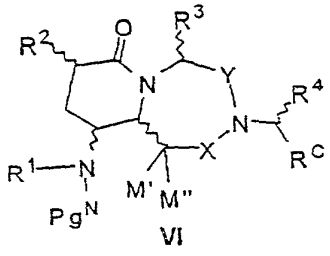
In relation to **Scheme 13**: 1,2 diols can be oxidised without carbon-carbon bond cleavage by the use of certain mild reagents e.g. IBX

(Frigerio and Sangostino, 1994). Conversion of **35c** to **36** proceeds by intramolecular reductive amination, or alternatively **35a** can be reductively aminated onto **2b**, as indicated. Reductive amination, coupling and deprotection details are as previously described.

The syntheses for the bicyclic □-turn mimetic systems **V** and **VI** are accomplished from the corresponding □-turn mimetic systems **I**, where the R^1 side chain group is derived from an aspartic acid (**V**) or glutamic acid (**VI**) derivative.



V



VI

	X	Y
V(i)	CH(M)	C(O)
V(ii)	C(O)	CH_2

	X	Y
VI(i)	CH(M)	C(O)
VI(ii)	C(O)	CH_2

The synthesis of mimetics **V** and **VI** thus proceeds as in Scheme 1, with the aldehyde component **1** (Scheme 1) being of the form **1d** or **1e** (Scheme 14), with the R and Pg groups as previously defined. The synthesis follows the synthesis of □-turn mimetic systems **I**, and is completed by the method illustrated in Scheme 15.

In relation to the preparation of alkylated aspartic and glutamic acid derivatives **1d** and **1e** the alkylated derivatives **39-42** can be prepared by a number of methods known in the art. Selected methods are summarised in Schemes 16 and 17. Rapoport and co-workers have developed methods for the selective alkylation of N-phenylfluorenyl protected aspartic and glutamic acid derivatives (Koskinen and Rapoport, 1989; Wolf and Rapoport, 1989). A review by Sardina and Rapoport, and references contained therein, describe several methods for the synthesis of alkylated aspartic and glutamic acid derivatives, incorporated herein by

reference (Sardina and Rapoport. 1996). Derivatives **39-42** are converted to aldehydes **1d** and **1e** by the methods previously described for for the preparation of aldehydes **1**.

The use of standard chemical techniques, in particular the Arndt-Eistert homologation reaction (Meier and Zeller, 1975) and reductions of carboxylic acids to aldehydes (Jurczak and Golebiowski, 1989), and also the synthesis of ketones -C(O)R from amides -C(O)N(OMe)Me (Nahm and Weinreb, 1981), to modify the aspartic and glutamic acid or their alkylated derivatives, or the use of similar derivatives of non-natural amino acids, such as homo-glutamic acid, enables the synthesis of the other compounds of the invention in which -Q^1Q^2- (in the general structure **X**) forms part of a cyclic system, defined as: -Q^1Q^2- = -$CH_2CH_2CH(R)C(O)$- (from sidechain alkylated homoglutamic acid); -$CH(R)CH_2$- (from aspartic acid by reduction of the □-carboxylate and reductive amination); -$CH_2CH(R)CH_2$- (from glutamic acid by reduction of the □-carboxylate and reductive amination); -$CH_2CH_2CH(R)CH_2$- (similarly from homoglutamic acid); -$CH_2CH(R)$- (from an aspartic acid sidechain ketone -$CH_2C(O)R$ by reductive amination); -$CH_2CH_2CH(R)$- (from a glutamic acid sidechain ketone -$CH_2CH_2C(O)R$ by reductive amination); -$CH(R)CH_2C(O)$- (post-alkylation sidechain homologated aspartic acid); -$CH_2CH(R)CH_2C(O)$- (post-alkylation sidechain homologated glutamic acid); -$CH(R)CH_2CH_2$- or -$CH_2CH(R)CH_2CH_2$- (from reductive amination of reduced post-alkylation sidechain homologated aspartic acid or glutamic acid derivatives).

In relation to **Scheme 18**: An alternative procedure for the synthesis of intermediate compounds **10** (or equivalent) can be used in the case where R^1 is hydrogen and M, M' and M'' are also hydrogen, as described in Scheme 18. Compound **49** is available commercially with certain N-protecting groups or can be made by coupling N-protected glycine with N,O-dimethylhydroxylamine. Reaction with vinylmagnesium bromide in analogy to the general procedure of Rapoport and co-workers

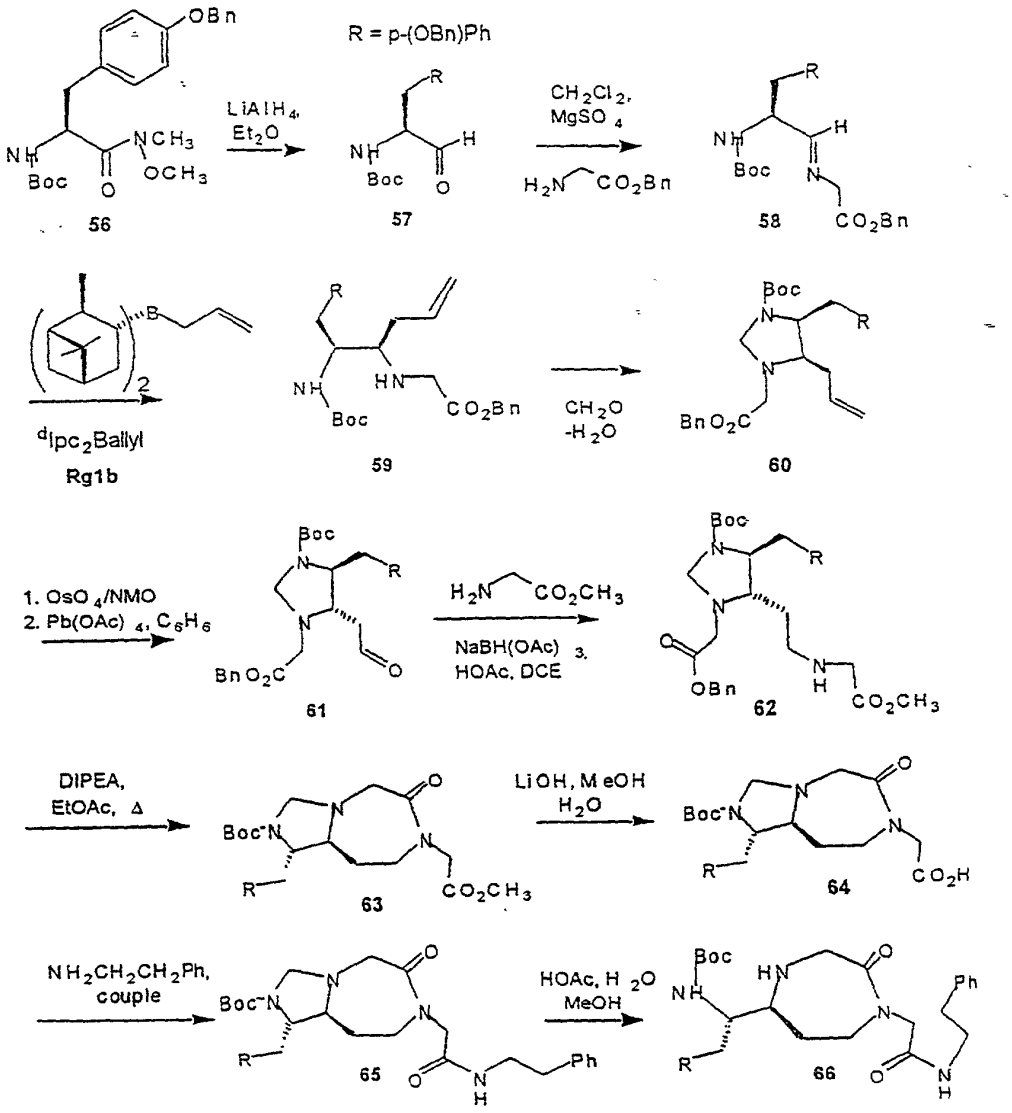
(Cupps *et al.*, 1985; Boutin and Rapoport, 1986) results in formation of the □,□-unsaturated ketone **50**. Conjugate addition of an amino acid ester **9** (0_C, THF) results in the formation of aminoketones **51** which can be N-protected by standard procedures to form ketones **52** before reductive amination of an amino acid ester **9** under the conditions described by Abdel-Magid *et al.* (Abdel-Magid *et al.*, 1996) ($NaBH(OAc)_3$, dichloroethane) to form **54**. Deprotection to **55** and coupling gives the □-turn mimetics **I(i)a** (where R^1=H) as indicated. Alternatively the aminoketones **51** can be acylated with an amino acid fluoride **15** to give compounds **53** which can be deprotected and cyclised (by reductive amination) by hydrogenation in mild acid conditions (H_2/Pd-C, 0.1M HCl in EtOH). The reductive amination-cyclisation is diastereoselective, only one diastereomer of the mimetics **I(i)a** were formed from **53**, with the configuration at the new stereocentre controlled by the R^2 stereocentre. The (S) configuration at R^2 gives (S) at the new centre. In contrast, the reductive amination to form amines **54** proceeds with lower stereoselectivity (~3:1) with the major diastereomer having the (R) configuration when R^2 is (S). These discoveries provide further opportunity for stereocontrol in the synthesis of the turm mimetics. Deprotection of compounds **54** and reaction with formalin in THF is an alternative method for synthesis of compounds **10** (R^1=H), as described in Scheme 18.

EXAMPLE SYNTHESES

Example (A). *Synthesis of a □-turn mimetic I(i) by the general procedure*

A mimetic for the sequence HTyr-Gly-Gly-Phe, which is found in the enkephalins, was synthesised with a □-turn mimetic based on the Tyr-Gly-Gly tripeptide. Similar mimetics have shown activity at opiate receptors (Huffman, Callahan *et al.*,1988; Huffman *et al.*, 1989).

The synthesis is summarised in the following scheme:-



Preparation of **56**:

The amide **56** was synthesised from commercially avaliable Boc-Tyrosine(OBn)OH by coupling with N,O-dimethylhydroxylamine hydrochloride, 1 equivalent, in DMF/CH_2Cl_2 (1:5) using HBTU reagent (1 eq.) and DIEA (2 eq.) at room temperature. The CH_2Cl_2 was evaporated *in vacuo* and the residue partitioned between diethyl ether and aq. $NaHCO_3$. The aqueous layer was separated and the ether layer washed in turn with 1M HCl (x2), aq. $NaHCO_3$, brine, and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the product amide **56** as a white crystalline solid in >90% yield. Further purification was carried out by silica gel chromatography eluting with ethyl acetate in petroleum ether, or by recrystallisation from ether. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.46-7.28, 5H, m, OBn; 7.08, 2H, d, J=8.5 Hz, Tyr Ar; 6.90, 2H, d, J=8.5 Hz, Tyr Ar; 5.15. bd, J=8 Hz, NH; 5.04, 2H, s,)OCH_2Ph; 4.91, 1H, bm, Phe□; 3.65, 3H, s, OCH_3; 3.16, 3H, bs, NCH_3; 3.00, 1H, dd, J=6, 13.5 Hz, Phe□; 2.83, 1H, dd, J=7, 13.5 Hz, Phe□; 1.40, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 172.3; 157.6, Tyr Ar-O; 155.1, carbamate; 137.0, ipso; 130.4; 128.8; 128.5; 127.8; 127.4; 114.7; 79.5, tBoc; 69.89, OCH_2Ph; 61.43, Tyr□; 51.55, OCH_3; 37.89, NCH_3; 32.00, Tyr□; 28.26, Boc.

Preparation of **57**:

The aldehyde **57** was prepared by the method of Fehrentz and Castro (Fehrentz and Castro, 1983) as follows: to a stirred solution of 4.2 g of amide **56** in 100 mls of anhydrous diethylether cooled to 0°C was added 0.51 g lithium aluminium hydride. After 10 minutes a solution of 1.5g $NaHSO_4$ in 30 mls of water was added. The reaction mixture was diluted with more ether and washed with 1M HCl, saturated aqueous sodium bicarbonate and brine and dried over magnesium sulphate. The volatiles were removed under reduced pressure to give a waxy solid which was recrystallised from cold ether/hexane to give 2.6 g (72%) of **57** as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 9.62, 1H, s, aldehyde; 7.50-7.25, 5H, m, Ar(OBn); 7.10, d, J=8 Hz, Ar(Tyr); 6.93, 2H, d, J=8 Hz,

Ar(Tyr); 5.10, 1H, b, NH; 5.05, 2H, s, OCH_2Ph; 4.39, 1H, q, J=7 Hz; Tyr□; 3.06, 2H, d(ABX), J=7 Hz, Tyr□; 1.44, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 199.6; 157.8, TyrOAr; 155.3, carbamate; 136.9, ipso; 130.3; 128.5, 127.9, 127.4: ArCH; 115.0, ArCHTyr; 80.08, tBoc; 69.69, OCH_2Ph; 60.82, Tyr□; 34.51, Tyr□; 28.22, Boc.

Preparation of **58**:

The imine **58** was formed by the reaction of the aldehyde **57** (1.4 g) with one equivalent of glycine benzyl ester in 10ml CH_2Cl_2 (stir at room temperature 1 h) the water formed was removed with magnesium sulphate which was then removed by filtration.

^1H NMR (300 MHz, $CDCl_3$): □ 7.68, 1H, s, imine; 7.49-7.30, 10H, Ar; 7.15, 2H, d, J=8 Hz, TyrAr; 6.92, 2H, d, J=8 Hz, TyrAr; 5.67, 1H, bd, J=6 Hz, NH; 5.20, 2H, s, OCH_2Ph; 5.05, 2H, s, OCH_2Ph; 4.51, 1H, bm, Tyr□; (4.26, 4.22), 2H, AB, J=15.5 Hz, Gly□; 3.15, 1H, bdd, J=5.0, 13.5 Hz, Tyrb; 2.93, 1H, dd, J=8.0, 13.5 Hz, Tyrb; 1.48, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 169.3; 167.4, CH imine; 157.5; 155.1; 136.9, 135.3: 2x ipso; 130.4, CHAr; 128.8, Tyr ipso; 128.44, 128.39, 128.26, 128.19, 127.76, 127.29, 114.65: ArCH; 79.22, tBoc; 69.81, Tyr**O**CH_2Ph; 66.60, GlyOCH_2Ph; 60.48, Tyr□; 54.73, Gly□; 37.97, Tyr□; 28.23, Boc.

Preparation of **59**:

A 0.5 molar solution of allyl borane reagent $^d Ipc_2Ballyl$ (**Rg1b**) was prepared by the addition of allylmagnesium bromide to one equivalent of (+)DIP-Cl in anhydrous diethyl ether under dry nitrogen. Brown and Jadhav, 1983). The solution of imine **58** in CH_2Cl_2 was stirred and cooled to -78°C under dry nitrogen and one equivalent of the previously prepared $^d Ipc_2Ballyl$ solution added. The mixture was allowed to warm gradually to room temperature (overnight). The volatiles were removed under reduced pressure and the residue dissolved in THF and 1 ml of glacial acetic acid added. The mixture was refluxed overnight and then the volatiles removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 / petroleum ether and the precipitate filtered off.

The residual oil was chromatographed on flash silica eluting with ethyl acetate / petroleum ether to give 1.3 g (60% yield based on **57**) of **59**. TLC 1:2 EtOAc:light pet. Rf=0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.48-7.30; 10H, Ar; 7.13, 2H, d, J=8.5 Hz, TyrAr; 6.91, 2H, d, J=8.5 Hz, TyrAr; 5.84, 1H, m, vinyl CH; 5.17, 2H, s, TyrOCH_2Ph; 5.16, 2H, m, vinyl CH_2; 5.05, 2H, s, GlyOCH_2Ph; 4.90, 1H, bd, J=8.5 Hz, NHBoc; 3.95, 1H, bm, Tyr□; 3.54, 2H, s, Gly□; 3.82, 1H, dd, J=4.5, 14.4 Hz, Tyr□; 2.73, 3H, be; NH(amine), Tyr□, CH(homoallyl); 2.28, 2H, m, allyl; 1.35, 9H, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 172.1; 157.3; 155.6; 137.1, 135.4: ipso; 134.9, CHvinyl; 130.6, ipsoTyr; 130.0, 128.5, 128.4, 128.3, 127.8, 127.3: ArCH; 117.8, CH_2vinyl; 114.7, TyrArCH; 79.05, tBoc; 69.90, TyrOCH_2Ph; 66.51, GlyOCH_2Ph; 59.38, Tyr□; 53.46, CH; 49.28, Gly□; 35.44: coincident allyl carbon and Tyr□; 28.20, Boc. Mass Spectrum (ISMS) m/z 545.1 (MH^+), calculated for $C_{32}H_{45}N_3O_5$: 544.

Preparation of **60**:

The amine **59** (930 mg, 1.7 mmol) was dissolved in ethyl acetate (15 mL) and 37% aq. formaldehyde solution added (1 mL). The solution was stirred vigorously at room temperature for 1 h (or until the reaction was complete) and then diluted with ether (100 mL) and washed in turn with aq. $NaHCO_3$, water (x3), brine and then dried ($MgSO_4$). Removal of solvent *in vacuo* left an approximately quantitative yield (950 mg) of the crude product **60** which was used in the next reaction or further purified by flash chromatography eluting with 10-15% ethyl acetate in light petroleum. TLC 33%EtOAc:light pet. Rf=0.56. The NMR spectra were quite broad in $CDCl_3$, amide rotamers were present in the approximate ratio 2:1. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.50-7.27, 10H, m's, Ar; 7.09, 2H, m, Ar; 6.90, 2H, d, J=8.5 Hz, Ar; 5.64, 1H, bm, vinyl CH; 5.19, 2H, s, OCH_2Bn; ~5.1, 2H, m, vinyl CH_2; 5.05, 2H, s, OCH_2Bn; 4.59, 1H, bm, ring NCH_2N(a); 4.17, 1H, bm, ring NCH_2N(b); 4.06, 1H, bm, Tyr□; 3.70, 1H, d, J=17 Hz, Gly□(a); 3.42, 1H, bd, J=17 Hz, Gly□(b); 3.16, 1H, bm, TyrC'H(ring); 2.84, 2H, bm, Tyr□; 2.31, 2H, m, allylCH_2; 1.38, ~3H, bs, Boc minor rotamer; 1.19, ~6H, s, Boc major rotamer. **^{13}C NMR** (75 MHz,

$CDCl_3$): □□□(peaks due to the carbamate rotamers are placed in parentheses, major rotamer first) 169.8 (ester); 157.2 (tyrosine O-ipso); (153.1, 152.8) carbamate; 137.2 (ipso); 135.4 (ipso); 134.2 (CH vinyl); 131.3 (ipso); 130.5, 128.5, 128.4, 128.3, 127.8, 127.4, 127.3, 126.9: ArCH; 117.5 (vinyl CH_2); 114.7 (2xTyrArCH); 79.52 (Boc tertiary); 69.93 (CH_2); 66.95 (CH_2); 66.46 (CH_2); 64.27 (CH); (59.65, 58.76) (CH); 51.60 (CH_2); 34.34 (CH_2); (32.20, 31.93) (CH_2); (27.93, 28.25) (Boc 3xCH_3). Mass Spectrum (ISMS) m/z 557.1 (MH^+), calculated for $C_{34}H_{40}N_2O_5$: 556 fragments (OR 60): 501.1, (-tBu).

Preparation of **61**:

To 220 mg of **60** was added 60 mg of N-methylmorpholine-N-oxide (NMO), 40 mg of a 2.5% (by weight) solution of osmium tetroxide in *t*-butanol, 4 mls of *t*-butanol and 0.5 mls water. The mixture was stirred at room temperature until the reaction was complete (about 24 hours). 3 mls of 10% $NaHSO_3$ was added, the solution stirred for 10 minutes, then neutralised with sodium bicarbonate, diluted with brine and extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. Removal of volatiles under reduced pressure gave the crude diol in good yield as an oil which could be used in the next reaction or purified if required by chromatography on silica gel eluting with ethyl acetate. Mass Spectrum (ISMS) m/z 591.3 (MH^+), calculated for $C_{34}H_{42}N_2O_7$: 590.

Oxidation of diol using $Pb(OAc)_4$: The diol (100 mg, 0.17 mmol) was dissolved in dry benzene (4 mL) and $Pb(OAc)_4$ (85 mg, moistened with acetic acid) was added. After 10 min stirring at room temperature the reaction was filtered, the solvent removed *in vacuo* and the residue purified by flash chromatography eluting with 25%EtOAc in light petroleum. Yield of the aldehyde **61** was 32% (30 mg). (No efforts to optimise the yield were made. Yield might be improved, for example, by partitioning the crude reaction mixture between aq.base and EtOAc to ensure none of the amine product was lost on filtration of the insoluble salts.) TLC 50%EtOAc in light pet. Rf=0.51. NMR analysis (NOESY

experiment) indicated the 4,5-trans ring conformation (i.e. the 4(S) isomer). **^{1}H NMR** (300 MHz, $CDCl_3$): □ 9.52, 1H, t, J=1.5 Hz, aldehyde; 7.50-7.25, 10H, m, ArH; 6.92, 2H, d, J=9 Hz, TyrAr; 5.15, 2H, s, OCH_2Ph; 5.05, 2H, s, OCH_2Ph; 4.65, 1H, bm, ringCH_2(i); 3.88, 1H, bm, Tyr□; 3.80, 1H, bm, ringCH_2(ii); 3.45, 1H, d, J=16 Hz, Gly□; 3.44, 1H, m, ringCH(□aldehyde); 3.28, bd, J=16 Hz, Gly□; 3.17, 1H, bm, Tyr□; 2.80, 1H, dd, J=9.0, 13.5 Hz, Tyr□; 2.51, 1H, J=6, 17 Hz, □aldehyde; 2.28, 1H, dd, J=17, 4.5 Hz, □aldehyde; 1.50, 9H, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$), (rotamers): □ 200.5; 169.9; 157.5; 153.1; 136.9; 135.3; 130.5, 129.6, 128.6, 128.5, 128.4, 127.6, 127.4, 115.0: Ar; 80.21, tBoc; 69.92, OCH_2Ph; (67.08, 66.86) br, CH_2; 66.58, OCH_2Ph; (62.93, 62.56) br, CH; (61.35, 60.72) br, CH; 52.14, CH_2; 46.36, CH_2; (38.5, 37.27) br, CH_2; 28.38, Boc. Mass Spectrum (ISMS) m/z 559.1 (MH^+), calculated for $C_{33}H_{38}N_2O_6$: 558.

Preparation of **62** and **63**:

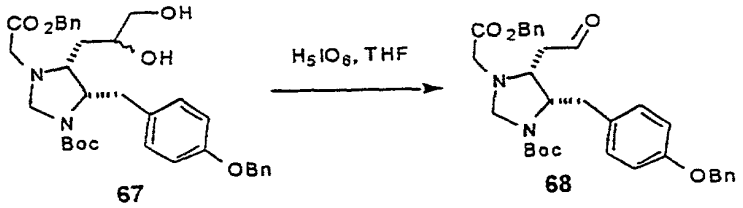
The aldehyde **61** (30 mg, 50□mol) was dissolved in 1.2-dichloroethane (5 mL) and glycine methyl ester hydrochloride (50 mg) and $NaBH(OAc)_3$ (50 mg) added. The reaction was stirred at room temperature and was complete in a few minutes (<15 min). The reaction was diluted with ethyl acetate, and washed in turn with aq.$NaHCO_3$, water, brine and then dried ($MgSO_4$). Evaporation of the solvent left the crude product **62** as a clear oil: TLC 1:1 EtOAc:light pet. Rf=0.17. Mass Spectrum (ISMS) m/z 632.3 ($M+H^+$), calculated for $C_{32}H_{45}N_3O_5$: 631 Analysis of the product or the reaction mixture after overnight standing revealed the formation of a new product with a mass spectrum corresponding to the target cyclised material **63** (MH^+=524Da). Thus the amine product **62** was not generally isolated but converted directly to **63**. The spontaneous cyclisation was accelerated by the addition of base (*i*-Pr_2NEt). After removal of solvent by evaporation under reduced pressure and the product was purified by flash chromatography eluting with 10-20% EtOAc in light pet. TLC: 1:1 EtOAc:light pet. Rf=0.51. **^{1}H NMR** (300 MHz, CD_3CN): □ 7.47-7.29, 5H, m, ArH; 7.12, 2H, m, Tyr; 6.92,

2H, m, Tyr; 5.07, 2H, s, OCH_2Ph; 4.35, 1H, d, J=5.4 Hz; AB_q, δ_a=4.05, δ_b=4.02, J_{AB}=17.4 Hz; 3.70-3.52, 6H, overlapped signals (includes: 3.65, 3H, s; 3.58, 1H, dd, J=11.2, 15.2 Hz); 3.49-3.32, 2H, br m's; 3.15, 1H, br dd, J=5.5, 15.5 Hz; 2.99, 1H, br dd, J=13.4, 14.9 Hz; 2.80, 1H, vbr m; 2.68, 1H, vbr m; 1.64, 1H, m; 1.46, 10H, s + m, Boc resonance obscures multiplet. **^{13}C NMR** (75 MHz, CD_3CN), rotamers, in approximate ratio 3:2, split some peaks and are recorded in parentheses: δ 173.3; 171.5; 158.8; 155.0, br; 138.9; 132.0; 129.9; 129.2; 129.0; 116.1; 80.84; 71.01; (70.87, 69.99); (68.12, 67.45); (65.47, 64.89); 55.76; 52.93; 51.45; 49.95; (39.00, 37.53); 31.87; 28.97 (Boc). Mass Spectrum (ISMS) m/z 524.3 (MH^+), calculated for $C_{29}H_{37}N_3O_6$: 523.

Preparation of compounds **64** to **66**:

The product **63** was hydrolysed with $LiOH/H_2O$/MeOH to the acid **64** (mass spectrum MH^+=510) and then coupled (DMF/CH_2Cl_2/HBTU/DIEA) with phenethylamine using standard procedures and work-up to give **65**. The imidazolidine ring of **65** was deprotected with a solution of acetic acid-methanol-water (~1:1:1, stirred as a very dilute solution for several days then lyophilised) to give crude **66** as a white amorphous solid. Mass Spectrum (ISMS) m/z 601 ($M+H^+$), calculated for $C_{35}H_{44}N_4O_5$: 600.

Example (B). *Synthesis of a (4,5)-cis imidazolidine aldehyde by oxidation of a diol.*

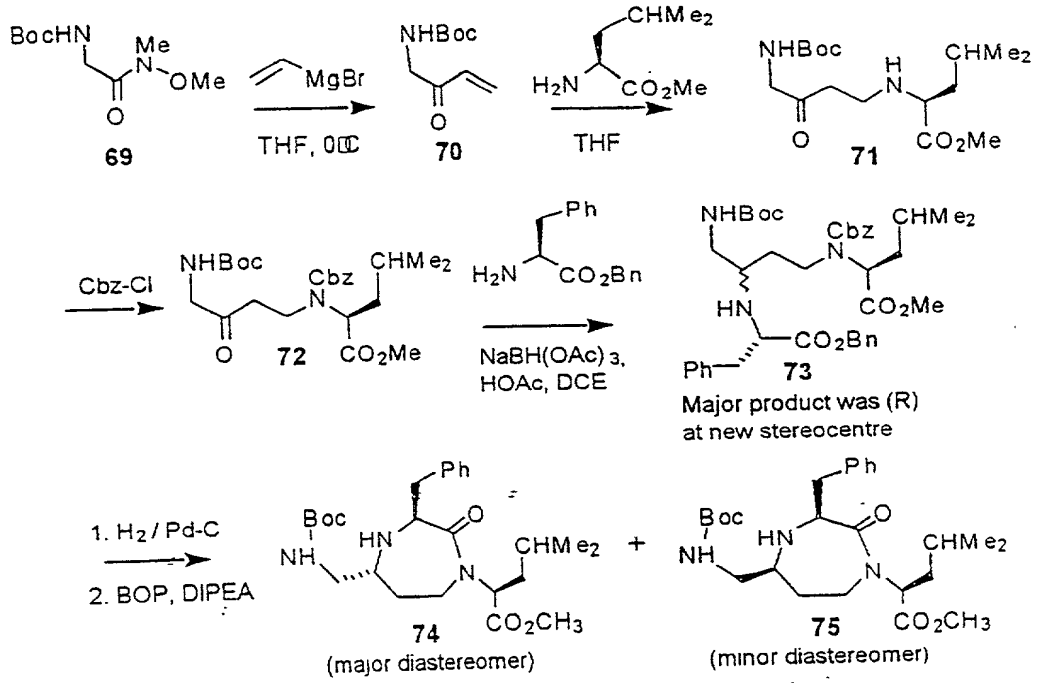


67 68

For the preparation of the 4,5-cis aldehyde **68** (in this case the 4(R) isomer) the diol **67** prepared from alkene **60** (as described above) (1mmol) was dissolved in THF (10 mL) and H_5IO_6 (1 mmol)

dissolved in THF (~20 mL) was added and the reaction stirred at room temperature. A precipitate of iodic acid rapidly formed and the reaction was complete in <5 min. The THF solution was diluted with ether and washed in turn with 10% aq.Na_2CO_3, water, brine and then dried ($MgSO_4$). The product aldehyde **68** was formed in good yield and purity. Contact with acid should be minimised to prevent isomerisation to the trans aldehyde and/or decomposition, for example avoid chloroform as an NMR solvent unless recently made acid free. Yield was 60-80%. TLC: 50%EtOAc in light pet. Rf=~0.5. **^{1}H NMR** (300 MHz, CD_3CN): □ (peaks moderately broad; the Boc rotamers were not resolved although the Boc peak was asymmetric and very broad) 9.48, 1H, bm, aldehyde; 7.5-7.3, 10H, m, 2xBn; 7.09, 2H, bd, J=7.5 Hz, Tyr Ar; 6.88, d, 8.2 Hz, Tyr Ar; 5.13, s, 2H, OCH_2Ph; 5.05, s, 2H, OCH_2Ph; 4.38, 1H, d, 6.0 Hz, NCH_2N(a); 4.22, 1H, m, Tyr□; 4.02, 1H, br, NCH_2N(b); 3.56, 1H, bd, J=17.2 Hz, Gly□(a); 3.48, 1H, m, TyrC'H; 3.29, 1H, bd, J=17.2 Hz, Gly□(b); 2.57-2.88, 4H, e, Tyr□ CH_2 and □-aldehyde CH_2; 2.22, s, H_2O; 1.48-1.08 (1.20 peak), 9H, vbr, Boc 3xCH_3. **^{13}C NMR** (75 MHz, CD_3CN): □ 201.9; 171.4; 158.7; 154.3; 139.0; 137.6; 132.6; 131.9, 129.92, 129.85, 129.6, 129.2, 128.9, 116.0: ArCH; 80.41 (Boc tert.); 70.99 (CH_2); 67.62 (br, CH_2); 67.44 (br, CH_2); 60.29 (2xCH, co-incident peaks determined by comparative intensity); 52.99 (br, CH_2); 43.58 (br, CH_2); 35.94 (br, CH_2); 28.78 (br, Boc 3xCH_3).

Example (C). *Synthesis of □-turn mimetics **I(i)** for the Gly-Phe-Leu sequence by the short method (which can be used when R^1 = hydrogen)*



Preparation of **69**:

Boc-glycine was coupled with N,O-dimethyl hydroxylamine hydrochloride, 1 equivalent, in DMF/CH_2Cl_2 (1:5) using HBTU reagent (1 eq.) and DIEA (2 eq.) at room temperature. The CH_2Cl_2 was evaporated *in vacuo* and the residue partitioned between diethyl ether and aq. $NaHCO_3$. The aqueous layer was separated and the ether layer washed in turn with 1M HCl (x2), aq. $NaHCO_3$, brine, and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the product amide **69** as a viscous oil that slowly crystallised to a waxy solid and was further purified by chromatography on silica gel. Yield was >90%. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 5.3, 1H, bs, NH; 4.09, 2H, bd, □H_2; 3.72, 3H, s, OCH_3; 3.20, 3H, s, NCH_3; 1.46, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 79.6; 61.4; 41.7; 32.4; 28.3.

Preparation of **70**:

A solution of 11.6 g (53 mmol) of Boc-glycine N,O-dimethylhydroxylamide in dry THF (70 mL) under nitrogen in a 250 mL round bottom flask was stirred and cooled in an ice bath. To this was added vinyl magnesium bromide in THF (~120 mmol of a 1M solution) by

syringe over 10 minutes. The solution was stirred for 2 h and then quenched by pouring into a mixture of crushed ice and 1M HCl which was then extracted with CH_2Cl_2 (x2). The organic extracts were washed with water/brine (x2), aq. $NaHCO_3$ and water/brine followed by drying over $MgSO_4$. Evaporation of the solvent left 9.6 g of a mobile oil (98% crude) which by NMR was ~95% the ketone product **70**. This material was used without further purification in the conjugate addition step. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 6.37, 2H, m (ABX, J_{ab}=2.5 Hz, $J_{ax/bx}$=9.0, 17.5 Hz), vinyl CH_2; 5.95, 1H, dd, J=2.5, 9.0 Hz, vinyl CH; 5.37, 1H, bs, NH; 4.26, 2H, d, J=4.6 Hz, glycyl □H_2; 1.46, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 194.9 ketone; 155.8 carbamate; 133.6 vinyl; 129.6 vinyl; 79.8 tBoc; 48.32 Gly□; 28.28 Boc.

Preparation of **71**:

To a solution of 3.0 g (~15 mmol) of crude **70** in THF (40 mL) was added 3.4 g of leucine methyl ester hydrochloride (~1.2 eq) and 2.4 g (1.2 eq) of diisopropylethylamine. After 2 h the reaction was diluted with ether (200 mL) and extracted with cold 1M HCl (3x50 mL) (discard this ether layer). The aq. extracts were immediately neutralised with solid $NaHCO_3$ and this solution was then back extracted with ether, and the ether washed with water (x3) and finally brine and dried over $MgSO_4$. Evaporation of the solvent left ~5.3 g of product **71** as an oil with very good purity, contaminated with a small amount of leucine methyl ester. Flash chromatography to separate the product was not very successful as the amine and amino ketone tended to co-elute. TLC EA/LP Rf=0.35. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 5.36, 1H, bm, NHBoc; 4.03, 2H, d, J=5 Hz, Gly□; 3.72, 3H, s, OCH_3; 3.26, 1H, t, J=7.5 Hz, Leu□; 2.93, 1H, dt, J=12, 6 Hz; 2.72, 1H, dt, J=12, 6 Hz; 2.50, 2H, m; 2.0, 1H, bs, NH; 1.69, 1H, m, Leu□; 1.45, 11H, m, Boc(9H) and Leu□(2H); 0.90, 6H, m, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 205.1; 176.1; 155.5; 79.8 tBoc; 60.04; 51.64; 50.53; 42.63; 42.57; 40.55; 28.26 Boc; 24.81; 22.63; 22.17. Mass Spectrum (ISMS) m/z 331.4 ($M+H^+$), calculated for $C_{16}H_{30}N_2O_5$: 330; fragments (OR 60): 275.2 (-tBu).

Preparation of **72**:

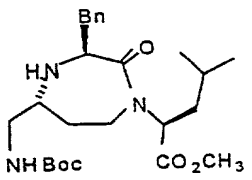
The amine **71** was protected as the benzyl carbamate by standard procedures as follows: the crude amine product **71** (1.68 g, ~5 mmol) was dissolved in ethyl acetate (30 mL) to which was added a solution of $KHCO_3$ (1.2 g) in water (15 mL). This mixture was vigorously stirred and cooled in an ice bath and to it was added benzyl chloroformate (780 uL of a 95% solution, 5.2 mmol) dropwise over 5 min. The reaction was stirred for a further 15 min then allowed to warm to room temperature with stirring for an additional 2 h. After this time the mixture was diluted with ether (100 mL), the aqueous layer seperated, and the organic layer washed with 1M HCl, aq. $NaHCO_3$, brine and then dried over $MgSO_4$. Evaporation of the solvent left ~2.6 g crude oil which was purified by flash chromatography eluting with 25%EtOAc in light pet; combination of the main fractions gave a yield of 86% (2.02 g) of **72**. TLC EA:2LP Rf=0.56.. NMR signals split due to amide rotamers (~1:1) are placed in parentheses where possible. **^{1}H NMR** (300 MHz, $CDCl_3$): □. 7.40-7.23, 5H, Ar; 5.28-5.02, 3H, m's, CH_2Ph + NH; (4.64, m, 4.43, m) 1H; (3.98, bs, 3.88, bs) 2H; 3.72-3.51, 4H, includes (3.67, s, 3.55, s) OCH_3 + 1H; 3.45, 1H, m; 2.78, 2H, m; 1.75, 2H, m; 1.53, 1H, m; 1.43, 9H, s, Boc; 0.91, 6H, m, Leu□ CH_3x2. **^{13}C NMR** (75 MHz, $CDCl_3$): □ (204.9, 204.5) ketone; (172.5, 172.3) ester; (156.1, 155.8) carbamate; 155.6, carbamate; (136.2, 136.0) ipso; 128.5, 128.2, 128.1, 128.0: ArCH; 79.80, tBoc; 67.48; (58.50, 58.32); 52.12; 50.30; (41.37, 39.87, 39.78, 38.87, 38.60, 37.98) 3C; 28.23, Boc; (24.83, 24.67); 23.09; (21.46, 21.39). Mass Spectrum (ISMS) m/z 465.3 (MH^+), calculated for $C_{24}H_{36}N_2O_7$: 464; fragments (OR 70): 409.2, (-tBu); 365.2, (-Boc).

Preparation of amines **73**:

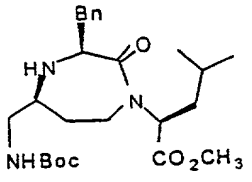
To a solution of **72** (700 mg, 1.5 mmol) in 15 mL of 1,2-dichloroethane was added phenylalanine benzyl ester p-toluene sulfonate (900 mg, 2.1 mmol) and sodium triacetoxy borohydride (850 mg, 4.0 mmol). The mixture was stirred at room temperature for 24 h and then the solvent removed under vacuum and the residue partitioned between ethyl

acetate and aq. $NaHCO_3$, the aqueous layer separated, and the organic layer washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent left 1.2 g crude oil which was purified by flash chromatography eluting with 25-40% EtOAc in light petroleum ether to give a yield of 76% (800 mg) of the product (a clear oil). The product diastereomers **73** were not seperable under these chromatography conditions. TLC 40%EA in LP Rf=0.48. **^{1}H NMR** (300 MHz, CD_3CN): □ (not very informative due to the presence of rotamers/diastereomers) 7.45-7.05 aromatic protons; (5.46 m, 5.31 m)~1/2H; 5.15-5.00, ~4H, m, OCH_2Ph; 4.95, ~1/4H, m; (4.51, m, 4.37, m): 1H; 3.85-3.10, ~5H, e (including 3.63, s, 3.58, s: 3H, OCH_3); 3.10-2.70, 5H, e; 2.45 broad water peak; 1.80-1.45, 5H, m's; 1.40, 9H, s, Boc; 0.90, 6H, bs, Leu□. **^{13}C NMR** (75 MHz, CD_3CN): □ (signals are grouped in parentheses where they can be reasonably assigned to equivalent carbons in the different diastereomers/rotamers) (175.6, 175.4(br)); 173.6; 157.4, 157.2 (br); (139.0, 139.2, 138.5, 138.3, 137.3) 3x ipso; 130.8, 130.7 129.9 129.71, 129.66, 129.3, 129.0, 128.0: Ar CH; (79.87, 79.62) Boc tertiary; 68.22 (CH_2, OBn); 67.75 (CH_2, OBn); (61.67, 61.55) (CH); 59.39 (CH); (56.51, 55.82, 55.61) (CH); 53.11 (OCH_3); (45.56, 45.16, 44.73, 44.61, 44.43, 44.24, 43.42, 43.04) (2xCH_2); (40.77, 40.15, 40.03, 39.42, 39.27) (2xCH_2); (39.66, 32.60, 32.45, 31.44) (CH_2); 29.04 (CH_3 Boc); 29.93 (CH); 23.88 (CH_2); 22.36 (CH_2). Mass Spectrum (ISMS) m/z 704.4 ($M+H^+$), calculated for $C_{40}H_{53}N_3O_8$: 703.

Preparation of **74** and **75**:



74 (R) - major product



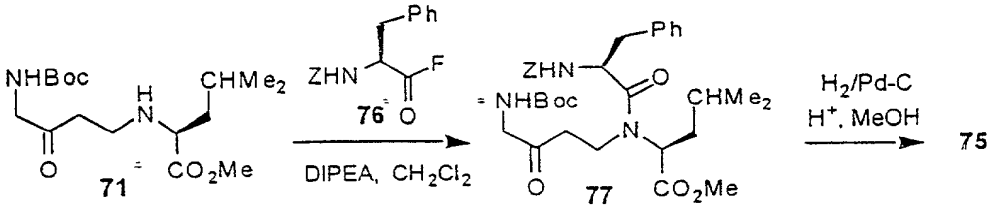
75 (S) - minor product

The mixture of epimeric amines **73** (260 mg, 0.4 mmol) was dissolved in methanol (20 mL) and 10% palladium on carbon added (100

mg). The solution was hydrogenated (40 psi H_2) at room temperature for 3 h to give the deprotected amino acid (MH^+=480Da). After filtration, the solvent was removed and the residue (170 mg) was dissolved in DMF (5 mL) and diluted with CH_2Cl_2 (50 mL). To this solution was added HBTU (180 mg, 0.48 mmol) and DIEA (150 mg, 1.2 mmol). After stirring for 10 min at room temperature the solution was diluted with aq.$NaHCO_3$, the aqueous layer separated, and the organic layer washed with water (x3) then brine and then dried over $MgSO_4$. Evaporation of the solvent left an oil which was purified by flash chromatography eluting with 20-40% EtOAc in light petroleum ether. The product diastereomers were just separable under these conditions, with the minor diastereomer **75** eluting first to give a yield of 18% (30 mg) followed by the major diastereomer **74** in 50% (85 mg) yield. TLC EA:LP 1:1 Rf=0.43, 0.29. **^{1}H NMR** (300 MHz, CD_3CN): □□ **Isomer 75**: 7.29, 4H, m, ArH; 7.22, 1H, m, ArH; 5.17, 1H, dd, J=6.5, 8.4 Hz; 5.08, 1H, m; 3.65, 3H, s, OCH_3; 3.61, 1H, dd, J=11.4, 15.6 Hz; 3.27, 1H, ddd, J=1.5, 5.7, 15.9 Hz; 3.12, 1H, dd, J=4.5, 14.3 Hz; 2.98, 1H, bm; 2.72, 1H, m; 2.64, 1H, dd, J=9.9, 14.3 Hz; 2.57, 1H, bm; (2.17, H_2O); 1.68, 3H, m; 1.60, 1H, m, Leu□; 1.36, 9H, s, Boc; 1.16, 1H, m; 0.95, 3H, d, J=6.4 Hz, Leu□; 0.93, 3H, d, J=6.6 Hz. **Isomer 74**: 7.29, 4H, m, ArH; 7.22, 1H, m, ArH; 5.11, 1H, dd, J=5.6, 9.4 Hz; 4.29, 1H, br, NHBoc; 3.81, 1H, dd, J=4.6, 9.8 Hz; 3.65, 3H, s, OCH_3; 3.59, 1H, dd, J=10.8, 15.2 Hz; 3.19, 1H, dd, J=5.5, 15.2 Hz; 3.13, 1H, dd, J=4.5, 13.8 Hz; 2.94, 2H, m's; 2.71, 1H, m; 2.64, 1H, dd, J=10.3, 13.3 Hz; (2.17, H_2O); 1.76, 1H, m; 1.69, 2H, m; 1.57, 2H, m; 1.36, 9H, s, Boc; 0.93, 6H, d, J=6.5 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): □ Isomer **75** (5S): 175.2; 172.5; 155.9; 138.9; 129.3; 128.5; 126.4; 79.2; 60.91; 60.62; 55.65; 52.19; 45.70; 43.98; 38.12; 37.99; 33.46; 28.30, Boc; 25.01; 23.10; 21.93. Isomer **74** (5R): 175.1; 172.5; 155.7; 139.3; 129.3; 128.7; 126.8; 78.9; 56.01; 55.80; 53.05; 52.14; 42.07; 40.70; 38.01; 37.98; 31.51; 28.26, Boc; 25.03; 23.11 21.74. Mass Spectrum (ISMS) m/z 462.3 (MH^+), calculated for $C_{32}H_{45}N_3O_5$: 461 fragments (OR 70): 406.2 (-tBu).

Example (D). *Selective synthesis of the 3(S), 5(S) diastereomer **75** by the short method*

The 3(S)5(S) diastereomer, the minor product formed as described above, can be selectively synthesised by the use of an intramolecular reductive amination-cyclisation as described below:



Preparation of acyl fluoride **76**:

Z-phenylalanine acid fluoride was prepared by general literature methods (Carpino *et al.*, 1990; Wenschuh *et al.*, 1994) as follows: 1.1 equivalents of diethylaminosulfurtrifluoride (DAST) were added to ZPheOH in dry dichloromethane solution under nitrogen at 0°C. After stirring for 15 min the reaction was worked up by pouring onto iced water and separating the organic layer, washing once with cold water and then drying over $MgSO_4$. The product was purified by precipitation from ether/petroleum ether and dried *in vacuo*. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.36, 8H, m's; 7.28, 2H, m; 5.30, 1H, bd; J=7.5 Hz, NH; 5.13, 2H, s, OCH_2Ph; 4.85, 1H, m, □H; 3.20, 2H, m, □H_2. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 161.8, d, $^1J_{CF}$=370 Hz; 155.5; 135.7; 134.2; 129.1; 129.0; 128.5; 128.3; 128.1; 127.7; 67.36; 53.50, d, $^2J_{CF}$=59 Hz; 36.70.

Preparation of **77**:

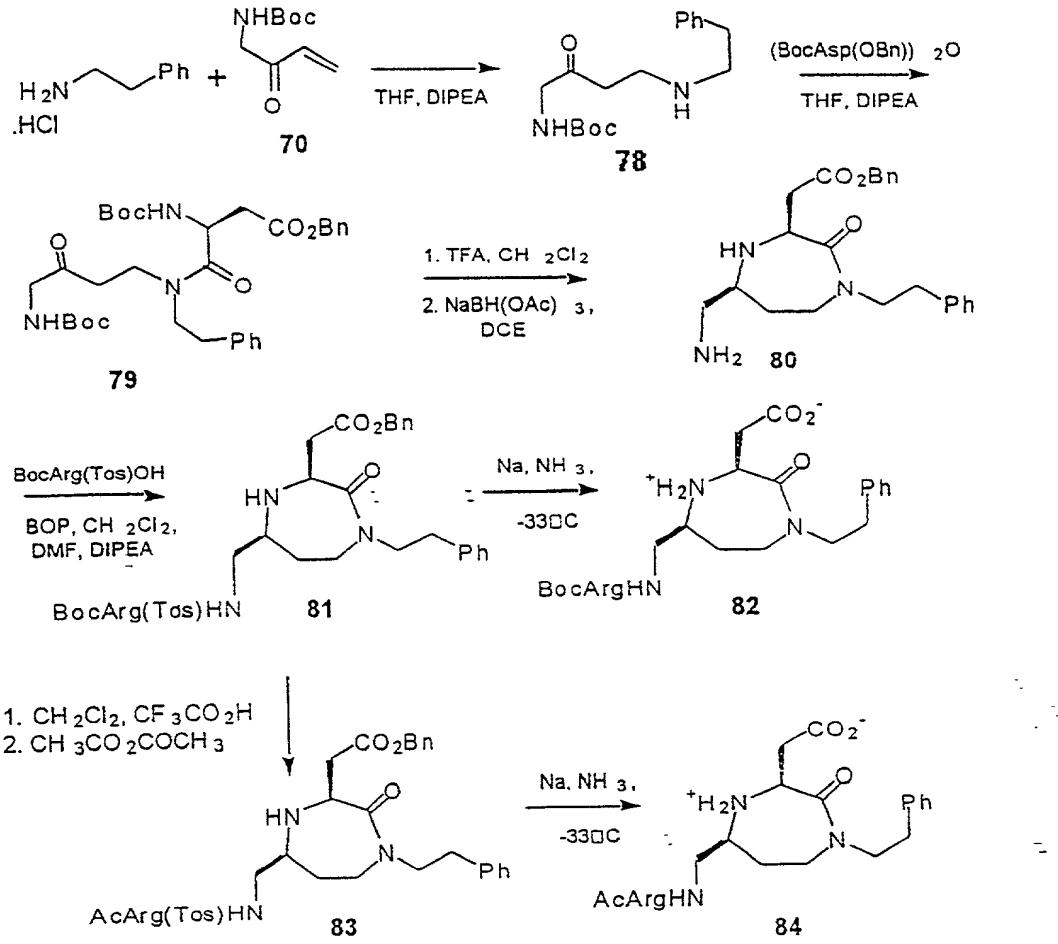
To the amine **71** (2.7 g, 8.2 mmol) dissolved in CH_2Cl_2 (40 mL) was added Z-phenylalanine acid fluoride **76** (prepared as described above) (3.0 g, 10 mmol) and DIEA (1.3 g, 10 mmol) and the solution stirred at room temperature under nitrogen for 30 h. The solvent was then evaporated *in vacuo* and the residue dissolved in ether and

extracted in turn with 1M HCl (x2), 10% aq. Na_2CO_3 (x2), then brine and then dried over $MgSO_4$. The solution was filtered and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography eluting with 20-40% ethyl acetate in light petroleum ether for a yield of about 80% of the target **77** as a clear oil. TLC 40%EA:LP Rf=0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.41-7.13, 10H, Ar; 5.48, 1H, bd, J=9.2 Hz, NHCbz; 5.19, 1H, bm, NHBoc; 5.09, 2H, s, OCH_2Ph; 4.76, 1H, dt, J=6.4, 8.9 Hz, Phe□; 4.38, 1H, dd, J=5.2, 9.3 Hz, Leu□; 3.92, 2H, d, J=4.5 Hz, Gly□; 3.60, 3H, s, OCH_3; 3.54, 1H, m; 3.38, 1H, m; 3.08, 1H, dd, J=8.4, 13.3 Hz; 2.93, 1H, dd, J=6.1, 13.1 Hz; 2.65, 2H, m; 2.80, 1H, m; 2.64, 1H, m; 1.46, 9H, s, Boc; ~1.38, 1H, m; 0.90, 6H, 2xd, J=6.6, 6.5, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$) amide rotamers (~5:1): only the major peak of rotamer peak pairs is reported: □ 204.1; 172.1; 171.4; 156.7; 155.6; 136.2; 135.8; 129.4-127.1: ArCH; 79.8; 66.82; 58.15; 52.25; 52.05; 50.28; 41.32; 39.58 (2 coincident signals as determined by relative intensity, shift and the presence of both minor rotamer peaks); 37.82; 28.23, Boc; 24.67; 23.08; 21.67. Mass Spectrum (ISMS) m/z 612.3 ($M+H^+$), calculated for $C_{33}H_{45}N_3O_8$: 611; fragments: (OR 60): 556.3 (-tBu); 512.3 (-Boc).

Selective preparation of **75** from **77**:

The ketone **77** (1mmol) was dissolved in 0.1M methanolic HCl (30ml) and 10% palladium on activated carbon (200mg) was added. The solution was hydrogenated at 30 psi H_2 (room temperature) for 8 h and then diluted with aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water (x2) and then brine then dried over $MgSO_4$. Filtration and removal of solvent in vacuo left the crude product **75** in good yield and purity. Analysis of the crude product by NMR and by TLC did not reveal any of diastereomer **74**. The reaction was estimated to be >95% stereoselective.

Example (E). *Synthesis of a biologically active □-turn mimetic for the Arg-Gly-Asp sequence*



Preparation of **78**:

The □,□-unsaturated ketone **70** (1.0 g, 5.4 mmol, prepared as previously described) was reacted with phenethylamine hydrochloride (1.07 g, 6.8 mmol) and DIEA in THF by the method previously described for the preparation of **71**. The crude product **78** was used without further purification for the next reaction. Mass Spectrum (ISMS) m/z 307.2 (MH^+), calculated for $C_{17}H_{26}N_2O_3$: 306; fragments (OR 60): 250.9 (-tBu).

Preparation of **79**:

To a stirred solution of Boc-aspartic acid □-benzyl ester (3.23 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dicyclohexylcarbodiimide (10 mL of 0.5M solution in CH_2Cl_2) at room temperature. A copious precipitate of dicyclohexylurea soom formed; after 10 min the solution was filtered, and the solvent removed *in vacuo*. The residual oil was

added to a solution of crude **78** (1.3 g) in THF, followed by DIEA (645 mg, 5 mmol), and the solution stirred for 4 h. The reaction mixture was diluted with ether/ethyl acetate and washed with 1M HCl, aq. $NaHCO_3$, water, brine and dried over $MgSO_4$. The crude product was purified by flash chromatography eluting with 30-50% ethyl ether in petroleum ether to give a reasonable yield of **79** (estimated as 80% based on **78**) as a clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$, amide rotamers present): □□ 7.38-7.16, 10H, m, Ar; 5.37. 1H, bd, J=9 Hz, AspNHBoc (minor rotamer 5.33, J=10 Hz); 5.25, m, 1H (Gly NH); 5.10, 2H, m, OCH_2Ph; 4.89, 1H, m; 3.93, 2H, d, J=4.4 Hz, Gly□; 3.67-3.53, 3H, m's; 3.47, 1H, m; 2.95-2.52, 6H, m's (including 2.88, 2H, m; 2.63, 2H, ABX, J=15.8, 7.3, 5.8 Hz, □H_2Asp); 1.44, 18H, multiple singlets, 2xBoc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ (major rotamer only) 204.7; 171.0; 170.3; 155.6; 154.8; 137.7; 135.5: 128.9, 128.6, 128.5, 128.2, 126.6: ArCH; 80.06; 79.73 (2x tBoc); 66.57; 50.55; 50.33; 46.99; 42.24; 37.69 (2 signals); 35.50; 28.22 (2x Boc). Mass Spectrum (ISMS) m/z 612.3 (MH^+), calculated for $C_{33}H_{45}N_3O_8$: 611 fragments (OR 60): 556.1 (-tBu); 512.1 (-Boc).

Preparation of **80**:

The ketone **79** (390 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) was treated with trifluoroacetic acid (2 mL) and the solution stirred for 30 min at room temperature. The volatiles were then removed *in vacuo* and CH_2Cl_2 (3 mL) added and removed *in vacuo* (x2). The residual oil was dissolved in 1,2-dichloroethane (5 mL) and $NaBH(OAc)_3$ (270 mg, 1.3 mmol) added. The mixture was stirred for 20 min then the solvent removed and the residue dissolved in ethyl acetate and washed with aq. Na_2CO_3 and then brine and then dried over $MgSO_4$. The crude product **80** (after solvent removal 210 mg, 84%) was of good purity by MS and NMR, with only one diastereomer observed (>95% diastereoselectivity). **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.39-7.10, 10H, m, Ar; {5.20, 5.16, 5.14, 5.10}, 2H, ABq, J=12.5 Hz) OCH_2Ph; 3.86, 1H, t, J=6.3; 3.76-3.43, 3H, m's; 3.14, 1H, bdd, J=15, 5 Hz; 2.98-2.76, 5H, e; 2.70, 1H, dd, J=7.4, 16 Hz; 2.46, 1H, m; 1.64, 1H, bm; 1.06, 1H bm. **^{13}C NMR** (75 MHz,

$CDCl_3$): □ 173.9; 172.0; 138.9; 135.9; 128.7, 128.4, 128.0, 126.3: Ar; 66.16; 60.49; 56.55; 51.24; 48.39; 45.14; 38.05; 34.15; 33.01. Mass Spectrum (ISMS) m/z 396.2 (MH^+), calculated for $C_{23}H_{29}N_3O_3$: 395.

Preparation of **81**:

The crude amine product **80** (140 mg, ~0.35 mmol) was coupled with BocArg(Tos)OH (182 mg, 1.2 eq) using the BOP reagent (188 mg) and DIEA (55 mg) in DMF/CH_2Cl_2 (5ml). The CH_2Cl_2 was evaporated *in vacuo* and the residue partitioned between diethyl ether/ethyl acetate and aq. $NaHCO_3$. The aqueous layer was separated and the organic layer washed in turn with 1M HCl (x2), water (x2), aq. $NaHCO_3$, brine, and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the crude product amide **81** which was purified by flash chromatography eluting with 5-10% ethanol in ethyl acetate (yield 260 mg, 90%). TLC 10% EtOH in EtOAc Rf=0.38. **^{1}H NMR** (300 MHz, CD_3OD): □ 7.74, 2H, d, J=7 Hz; 7.4-7.15, 12H, m's; 5.15, 2H abq, J=11 Hz, OBn; 4.26, 1H, m; 4.03, 1H, m; 3.73, 2H, m; 3.48-3.07, 7H, e; 3.07, 1H, m; 2.92-2.73, 3H, m's; 1.92, 1H, m; 1.73, 1H, m; 1.66-1.45, 4H, e; 1.42, 9H, s, Boc. **^{13}C NMR** (75 MHz, CD_3OD): □ 176.1; 172.5; 172.0 (br); 158.8; 158.1; 143.7; 142.2; 140.3; 137.5; 130.4; 130.1; 129.72; 129.68; 129.4; 128.4; 127.6; 127.3; 127.2; 80.92 (t); 67.75 (CH_2); 62.55 (CH); 57.27 (CH); 56.00 (CH); 52.55 (CH_2); 48.74 (CH_2); 44.42 (CH_2); 41.22 (br, CH_2); 37.00 (CH_2); 35.10 (CH_2); 32.41 (CH_2); 30.15 (CH_2); 28.87 (Boc CH_3); 27.24 (br, CH_2); 21.57 (CH_3). Mass Spectrum (ISMS) m/z 806.4 (MH^+), calculated for $C_{41}H_{55}N_7O_8S$: 805.

Preparation of **82**:

The amine **81** (50 mg, 0.06 mmol) in THF (0.6 mL) was cooled in a dry ice acetone bath and ammonia gas added until ~30 mL of ammonia had condensed. Small pieces of sodium metal (3-6 mg) were added until the blue colour persisted. The reaction was quenched by the addition of ammonium carbonate (25 mg), the dry ice bath removed and the solvent allowed to evaporate at room temperature. The residue (which gave a crude mass spectrum with the product mass as the only

significant peak) was purified by reversed phase HPLC (Vydac C18) eluting with 85% solvent A (=0.1% CF_3COOH in H_2O):15% solvent B (=0.1% CF_3COOH and ~10% H_2O in CH_3CN) for 2 minutes followed by a 2%/min gradient. Only one product diastereomer was observed in the HPLC traces. Mass Spectrum (ISMS) m/z 562.3 ($M+H^+$), calculated for $C_{27}H_{43}N_7O_6$.

Preparation of **83**:

The amine **81** was dissolved in CH_2Cl_2/CF_3CO_2H (2ml, 1:1) and stirred at room temperature for 30 minutes after which the Boc group had been removed. 10ml of CH_2Cl_2 was then added and the volatiles removed in vacuo (repeat once). The residue was again dissolved in CH_2Cl_2 and acetic anhydride (2 eq.) added along with diisopropylethylamine (DIEA, 5 eq.), and the reaction stirred at room temperature for 2 h. The volatiles were removed *in vacuo* and the residue dissolved in ethyl acetate and washed with aq. $NaHCO_3$ then brine and then dried over $MgSO_4$. Filtration and removal of the solvent *in vacuo* left the crude product **83** as an oil in reasonable purity. The ^1H NMR was badly broadened in common solvents at room temperature. **^{13}C NMR** (75MHz, $CDCl_3$): □ 173.7; 172.4; 171.9; 171.0; 157.0; 142.1; 140.4; 138.8; 135.8; 129.2, 128.7, 128.4, 128.1, 128.0, 126.3, 125.8: ArCH; 66.22, OCH_2Ph; 60.08, CH; 56.09, CH; 52.94, br, CH; 51.06, CH_2; 48.21, CH_2; 44.31, CH_2; 40.13, br, CH_2; 37.79, CH_2; 34.16, CH_2; 32.97, CH_2; (29.59, 29.50) 1C, br, CH_2; 25.64, br, CH_2; 22.91. CH_3; 21.32, CH_3. Mass Spectrum (ISMS) m/z 748.2 (MH^+), calculated for $C_{37}H_{49}N_7O_7S$: 747.

Preparation of **84**:

Compound **84** was prepared from **83** by dissolving metal reduction as described for the preparation of **82** above. Purification was carried out by HPLC under the same conditions as for **82**.

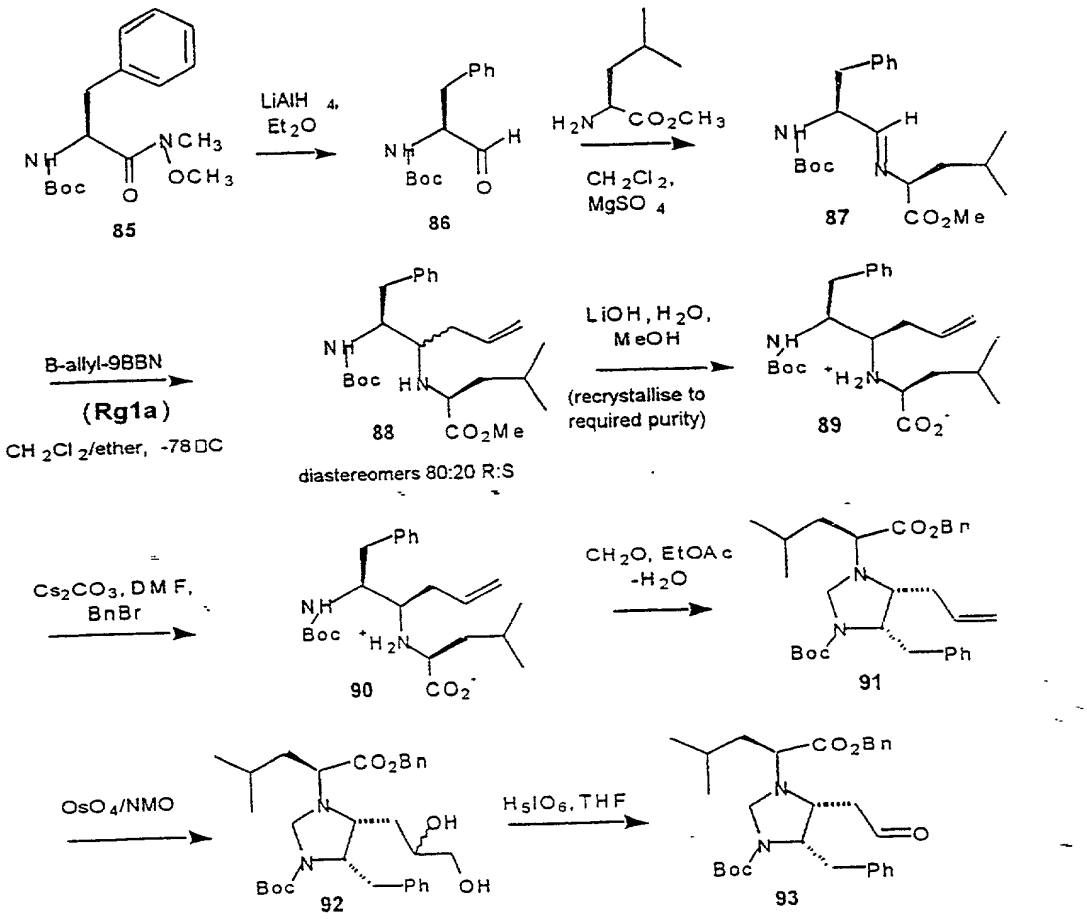
Testing of Arg-Gly-Asp mimetics 82 and 84 for inhibition of platelet aggregation in human platelet rich plasma (PRP)

The peptide sequence arginine-glycine-aspartic acid (RGD) is important to the binding of proteins to certain integrin receptors, such as the $GP_{IIb-IIIa}$ receptor found on the surface of platelets. Several cyclic peptides having the RGD sequence have been found to antagonise the binding of plasma proteins to the $GP_{IIb-IIIa}$ receptor, thereby inhibiting blood clotting. $GP_{IIb-IIIa}$ antagonists have therapeutic potential as anti-thrombotics, there are several in early clinical trials(Humphries, Doyle *et al.*, 1994). Mimetics based on □-turn structures centred on the Asp residue have been successful, this structure was chosen to test the compounds of the invention.

Solutions of the compounds to be tested were made up in water. Platelet aggregation induced by adenosinediphosphate (ADP, 10□M) in human PRP was measured by the decrease in light scattering on aggregation, measured with a platelet aggregometer. The tetra-peptide Ac-Arg-Gly-Asp-Ser-NH_2 was used as a positive control.(Callahan *et al.*, 1992) Compounds **82** and **84** were both found to inhibit platelet aggregation in a dose dependent manner, and both exhibited stronger inhibition than the control peptide. Compound **84** was the strongest, having inhibitory activity approximately five times more potent than Ac-Arg-Gly-Asp-Ser-NH_2 under the conditions of the test.

Example (F). *Synthesis of fully substituted □-turn mimetics for the Phe-Leu-Ala sequence in both the 4(R) and 4(S) configurations*

The synthesis up to the final common intermediate for the 4(R) and 4(S) diastereomers, the aldehyde **93**, is summarised below:-



Bocphenylalanine N,O-dimethylhydroxylamide **85** was synthesised by the general solution phase coupling procedure as previously described from Boc-phenylalanine and N,O-dimethyl hydroxylamine hydrochloride. Yield: ~quantitative. Purification: on a short silica column eluting with ether. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.33-7.12, 5H, m, Ar; 5.20, 1H, bd, J~7 Hz, NH; 4.95, 1H, bm, Phe□; 3.66, 3H, s, OCH_3; 3.17, 3H, s, NCH_3; 3.06, 1H, dd, J=6, 13.5 Hz, Phe□; 2.88, 1H, dd, J=7.5, 13.5 Hz; 1.40, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 172.2; 155.1; 136.5; 129.4; 128.2; 126.7; 79.5; 61.4; 51.4; 38.8, Phe□; 32.0; 28.2, Boc.

The amide **85** was reduced to Bocphenylalanine aldehyde **86** by the method of Fehrentz and Castro (Fehrentz and Castro, 1983) Briefly: amide (2 mmol) dissolved in dry ether (20 mL) and cooled and in

an ice bath under nitrogen, then $LiAlH_4$ (95 mg, 2.5 mmol) added and stirring continued 15 min. Then $KHSO_4$ (477 mg, 3.5 mmol) in 10 mL water added and then 150 mL ether and wash with 1M HCl (cold) (x3), aq. $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent left the solid aldehyde in ~90% crude yield containing some of the overreduced alcohol as the only significant impurity. TLC EtOAc:light pet. Rf=0.5. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 9.63, 1H, s, aldehyde; 7.37-7.13, 5H, m, Ar; 5.07, 1H, bs, NH; 4.43, 1H, m, Phe□; 3.11, 2H, d(AB) Phe□; 1.43, 9H, s, Boc. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 199.4, aldehyde; 155.3, carbamate; 135.7, ipso; 129.3, 128.7, 127.1: ArCH; 80.2, tBoc; 60.8, Phe□; 35.5, Phe□; 28.2, Boc

Methyl leucinate hydrochloride (0.80 g, 4.4 mmol) was neutralised with 10% aq. Na_2CO_3 solution (25 mL), and the solution was mixed with brine (25 mL) and extracted with CH_2Cl_2 (3x20 mL). The organic extracts were dried over $MgSO_4$ and most of the solvent removed under vacuum (~2 mL residue). This solution of methyl leucinate was added to Boc phenylalanine aldehyde **86** (1.1 g, 4.4 mmol) in CH_2Cl_2 (5 mL), the stirred solution soon became turbid due to the separation of water, dried $MgSO_4$ (500 mg) was added and the solution cleared. After 30 min the solution was filtered into a dried flask under nitrogen. NMR analysis showed that all the aldehyde had been converted to the imine **87** and that significant racemisation had not taken place. The imine was used without further purification for the allylation reaction. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.61, 1H, d, J=1.3 Hz, imine; 7.32-7.14, 5H, m, Ar; 5.69, 1H, bd, J=4.5 Hz, NH; 4.49, 1H, m, Phe□; 3.85, 1H, dd, J=5.5, 8.5 Hz, Leu□; 3.69, 3H, s, OCH_3; 3.20, 1H, dd, J=5.0, 14.5 Hz, Phe□; 2.96, 1H, dd, J=8.0, 13.5 Hz; Phe□; 1.63, 1H, m; 1.46, 9H, s, Boc; 1.42, 1H, m; 1.30, 1H, m; 0.88, 3H, d, J=6.5 Hz, Leu□; 0.80, 3H, d, J=6.5 Hz, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 171.7, ester; 164.3, CH, imine; 154.6, carbamate; 136.1, ipso; 128.9, 127.7, 126.0: ArCH; 78.56, tBoc; 69.51; 54.08; 51.32; 41.02, CH_2; 38.04, CH_2; 27.73, Boc; 22.35; 22.48; 20.63.

B-allyl-9-borabicyclononane **Rg1a** can be synthesised from B-methoxy-9-borabicyclononane (synthesised in turn from the methanolysis of 9-BBN (Kramer and Brown, 1974)) by the method of Kramer (Kramer and Brown, 1977). Alternatively the following one-pot synthesis from 9-BBN was used: a suspension of 9-BBN (crystalline dimer, 8.97 g, 73.5 mmol) in anhydrous ether (75 mL) was stirred under nitrogen and cooled to 0°C. Methanol (3.3 mL, 81 mmol) was slowly added by syringe (gas evolved), and vigorous stirring continued for ~3 h (9-BBN gradually dissolves, gas evolution ceases). Allylmagnesium bromide in ether (81 mL of a 1.0M solution) was slowly added to the solution (still cooled to 0°C); (a thick grey ppt. forms, stirring may be difficult). Stirring was continued for 1 h then the solution was allowed to warm to room temperature and the ether was pumped off under moderate vacuum (~300->20mbar). The residue was re-suspended in anhydrous hexane (100 mL) and then stirring stopped to allow the magnesium salts to settle out. The solution was estimated by reaction with a known amount of methylphenylketone in ether (found to be ~0.57M, equal to 78% yield). The clear solution of B-allyl-9-BBN was used directly for allylation of the imines. (This procedure was adapted from one described by Rachlera and Brown (Racherla *et al.*, 1992)) The imine **87** (~23 mmol) was dissolved in dry diethylether (100 mL) under nitrogen and the stirred solution cooled to -78°C. B-allyl-9-BBN (47.5 mL of ~0.57M solution in hexane, ~27 mmol) was added and the solution stirred for 1 h and then allowed to warm to room temperature with stirring for an additional 1 h. Glacial acetic acid (1.5 mL) was added and the ether was removed *in vacuo*. The residue was dissolved in acetonitrile (100 mL) and more glacial acetic acid (5 mL) added. The solution was then refluxed until all of the borane adduct had been converted to the amine (~24 h, monitored by TLC: Rf adduct>Rf amine = 0.32 in 1:5 EtOAc:light pet.). The acetonitrile was removed *in vacuo* and the residue partitioned between ether/light petroleum and 10% aq. Na_2CO_3. The organic layer was washed again with 10% aq. Na_2CO_3 and then extracted with a solution of

25% methanol in 0.5M HCl (three times), the organic layer containing the neutral reaction products (~6 g) was discarded. The aq. acid extracts were immediately neutralised with solid $NaHCO_3$ and then extracted with ether. The ether solution was washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent left the amine products (5.9 g) which were further purified by flash chromatography eluting with 7.5-15% ethyl acetate in light petroleum for a yield of 50+% of the amines **88** based on the crude aldehyde **86** used in the imine formation. Some separation of the diastereomers was observed in the chromatography, but they were not well resolved. Alternatively the crude amines were hydrolysed to the amino acid as described below and purified by recrystallisation. **^{1}H NMR** (300 MHz, $CDCl_3$), major diastereomer: □ 7.32-7.13, 5H, m, Ar; 5.84, 1H, m, vinylCH; 5.11, 2H, m, vinylCH_2: 5.00, 1H, d, J=8 Hz, NHBoc; 3.88, 1H, m, Phe□; 3.66, 3H, s, OCH_3; 3.40, 1H, t, J=7 Hz, Leu□; 2.87, 1H, dd, J=5, 13 Hz, Phe□; 2.69, 2H, m's: Phe□+CH(homoallyl); 2.23, 2H, m, allyl; 1.7, 1H, b, NH(amine); (1.65, 1H, m; 1.47, 2H, m) Leu□+□; 1.33, 9H, s, Boc; 0.90, 6H, t(2 doublets) J=7, 7 Hz, Leu□. **^{13}C NMR** (75 MHz, $CDCl_3$), major isomer: □ 176.1; 155.4; 138.6, ipso; 135.2, CH vinyl; 129.2, 128.2, 126.1: CHAr; 117.4, CH_2 vinyl; 78.8, tBoc; 58.94; 58.56; 54.10; 51.71; 42.87; 36.52; 35.61; 28.24, Boc; 24.78; 22.68; 22.23. Mass Spectrum (ISMS) m/z 419.2 (MH^+), calculated for $C_{32}H_{45}N_3O_5$: 418 fragments (OR 65): 363.2, (-tBu).

The crude amine product **88** (1.7 g, ~4 mmol) was dissolved in methanol/water and $LiOH.H_2O$ (800 mg, 19 mmol) added. The solution was stirred at room temperature until the hydrolysis was complete (12 h) and then neutralised with 1M HCl (19 mL). On standing a copious white precipitate formed which was filtered off and washed with water. The solid was recrystallised from ethanol-water (~95:5) to give fine needles of (mainly) the major diastereomer **89** (first crop 1 g), m.p.:175-177°C. The product was further recrystallised as required. **^{1}H NMR** (300 MHz, CD_3OD): □ (ref. 3.31 ppm) 7.33-7.18, 5H, m; 5.90, 1H, m; 5.35, 1H, d;

J=17.1 Hz; 5.26, 1H, d, J=10.2 Hz; 4.31, 1H, m; 3.65, 1H, dd, J=5.7, 7.9 Hz; 3.27, 1H, m; 2.92, 1H, dd, J=5.2, 14.0 Hz; 2.76, 1H, dd, J=10.1, 14.0 Hz; 2.59, 1H, m; 1.82, 1H, m; 1.37, 9H, s, (Boc); 0.97, 3H, d, J=7 Hz; 0.94, 3H, d, J=7 Hz. **^{13}C NMR** (75 MHz, CD_3OD): □ (ref. 49.15 ppm) 173.7; 159.4; 138.8; 134.5; 130.33; 129.8; 128.0; 120.5; 81.34; 63.65; 55.84; 41.19; 37.90; 32.70; 28.78; 26.11; 23.56. Mass Spectrum (ISMS) m/z 405 (MH^+), calculated for $C_{23}H_{36}N_2O_4$: 404.

The amino acid **89** was esterified to **90** by the method of Bodansky and Bodansky (Bodansky and Bodansky, 1984) as follows: the amino acid **89** (400 mg, 1 mmol) was dissolved in methanol/water and neutralised with Cs_2CO_3 (300 mg), then the solvents were removed *in vacuo*, then DMF added and removed *in vacuo*. The residue was dissolved in DMF (10 mL) and benzyl bromide (190 mg, 1.1 mmol, purified by passage through a short column of basic alumina) added to the stirred solution. After 2 h the reaction was diluted with aq. $NaHCO_3$ and extracted with 1:1 EtOAc:light pet. The organic layer was washed in turn with aq.$NaHCO_3$, water (x2), brine and then dried over $MgSO_4$. Evaporation of the solvent left the product **90** as a clear oil which solidified to a low melting solid (m.p. ~55°C) on standing (500 mg, ~100%). TLC 25%EtOAc in light pet. Rf=0.57. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.38-7.32, 4H, m; 7.28-7.14, 6H, m; 5.82, 1H, m; 5.19-5.05, 4H, m's, (OBn ABq, J=12.5 Hz, □a=5.16, □b=5.12 ppm); 4.9, 1H, br; 3.88, 1H, br; 3.44, 1H, bt, J=7 Hz; 2.88, 1H, dd, J=5, 14 Hz; 2.77-2.60, 2H, bm; 1.63, 1H, m; 1.56-1.35, m, 2H; 1.33, 9H, bs (Boc); 0.88, 3H, d, J=6.5 Hz; 0.85, 3H, d, J=6.5 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 175.5; 155.5; 138.6; 135.8; 135.2; 129.2; 128.5; 128.2; 126.1; 117.4; 78.90; 66.40; 58.96; 58.49; 54.25; 42.83; 36.33; 35.71; 28.27 (Boc); 24.77; 22.63; 22.32. Mass Spectrum (ISMS) m/z 495 ($M+H^+$), calculated for $C_{30}H_{42}N_2O_4$: 494.

The amine **90** (500 mg, 1 mmol) was dissolved in ethyl acetate (20 mL) and 37% aqueous formaldehyde solution (0.5 mL) was added. The solution was stirred for 12 h and then diluted with light

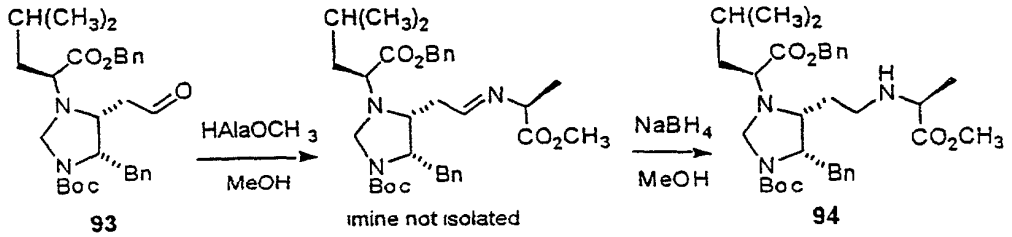
petroleum (40 mL) and washed in turn with aq. $NaHCO_3$, water (x2) and brine and then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the product **91** as a clear oil in approximately quantitative yield. Further purification was carried out by flash chromatography eluting with 10% ethyl acetate in light pet. **^{1}H NMR** (500 MHz, CD_3CN): □□ (rotamers were present in a ratio of 7:3) 7.36, 4H,m, Ar; 7.27-7.11, 6H, Ar; 5.70, 1H, m, vinyl CH; 5.17-4.97, 4H, m's, vinyl CH_2 and OCH_2Ph; 4.44. 0.7H, d, J=5.0 Hz, ring CH_2(a), major rotamer; 4.33, 0.3H, d, J=4.4 Hz, ring CH_2(a), minor rotamer; 4.19, 0.7H, d, J=5.0 Hz, ring CH_2(b), major rotamer; 4.09, 0.3H, d, J=4.6 Hz, ring CH_2(b), minor rotamer; 4.06, 0.3H, m, Phe□, minor; 4.02, 0.7H, m, Phe□, major; 3.74, 0.7H, dd, J=9.8, 6.0 Hz, and 3.69, 0.3H, m, Leu□; 3.10, 1H, m, ring methine (homoallyl); 2.88, 0.3H, m, Phe□(a); 2.84, 0.7H, dd, J=4.1, 13.4, Phe□(a); 2.72, 0.3H, dd, J=6.5, 13.5, Phe□(b); 2.65, 0.7H, dd, J=9.5, 13.2, Phe□(b); 2.49, 1H, m, allyl(a); 2.15, 1H, m, allyl(b); 1.76-1.42, 3H, m's, Leu□+□; 1.33, 2.5H, s, Boc, minor rotamer; 1.09, 6.5H, s, Boc, major rotamer; 0.97-0.84, 6H, d's, Leu□ (major rotamer: 0.94, J=6.3 Hz; 0.90, J=6.2 Hz). **^{13}C NMR** (75 MHz, CD_3CN), only major rotamer reported except where indicated: □ (ref. 118.69 ppm) 173.3; 154.2; 140.9; 137.8; 136.3 (CH); 131.3; 129.9; 129.7; 129.6; 129.5; 127.2; 118.2 (CH_2); 79.98 (Boc tertiary); 67.17 (CH_2); 63.49 (CH); 62.47 (CH_2); 60.91 (CH); 57.68 (CH); 40.34 (CH_2); 36.04 (CH_2); 33.18 (CH_2); (29.08 Boc minor rotamer); 28.61 (Boc major rotamer); 25.98 (CH); 23.79 (CH_3); 22.36 (CH_3). Mass Spectrum (ISMS) m/z 507 (MH^+), calculated for $C_{31}H_{42}N_2O_4$: 506.

The alkene **91** was dihydroxylated with OsO_4/N-methylmorpholine-N-oxide in tBuOH/water as previously described for the dihydroxylation of **60**. The crude product **92** was used directly in the next reaction. TLC 1:1 EtOAc:light pet. Rf=0.36. Mass Spectrum (ISMS) m/z 541 ($M+H^+$), calculated for $C_{31}H_{44}N_2O_6$: 540.

The glycol **92** (87 mg, 0.16 mmol) was dissolved in THF (4 mL) and H_5IO_6 (37 mg, 0.16 mmol) dissolved in THF (3 mL) was added

and the reaction stirred at room temperature. A precipitate of iodic acid rapidly formed and the reaction was complete in <5 min. The THF solution was diluted with ether and washed in turn with 10% aq.Na_2CO_3, water, brine and then dried ($MgSO_4$). The product aldehyde **93** was of good purity but was not particularly stable to storage. Any traces of acid must be rigorously excluded to prevent isomerisation to the trans isomer. A portion was purified by flash chromatography, eluting with 15%EtOAc in light petroleum. TLC 15%EtOAc in light pet. Rf=0.27. The yield was good (>80%). Amide rotamers were evident in the NMR spectra. ratio ~3:1, only the peak due to the main rotamer is reported unless otherwise noted. **^{1}H NMR** (300 MHz, CD_3CN, ref 1.94 ppm): □ 9.53, 1H, s; 7.42-7.10, 10H, m's; 5.11, 2H, s, (OCH_2Ph); 4.41, 1H, br; 4.25, 1H, q, J=6.3 Hz; 4.15, 1H, br; 3.56, 1H, dt, J=8.5, 5.7 Hz; 3.54, 1H, bm; 2.90-2.58, 4H, m; 1.75-1.45, 3H, bm; 1.37, bs, Boc minor rotamer; 1.20, bs, Boc major rotamer; 0.92, 3H, d, J=6 Hz; 0.88, 3H, d, J=5.7 Hz. **^{13}C NMR** (75 MHz, CD_3CN, ref 118.69 ppm): □ 202.0; 173.1; 154.2; 140.4; 137.6; 131.1; 129.9; 129.62; 129.55; 127.26; 80.28 (Boc tertiary); 67.31 (CH_2); 61.90 (CH_2); 60.43 (CH); 58.56 (CH); 57.95 (CH); 43.75 (CH_2); 40.36 (CH_2); 36.48 (CH_2); 28.66 (Boc); 25.83 (CH); 23.67 (CH_3); 22.25 (CH_3). Mass Spectrum (ISMS) m/z 509 (MH^+), calculated for $C_{30}H_{40}N_2O_5$: 508.

Conversion of 4,5-cis aldehyde **93** to the 4,5-cis 4(S) amine product was completed by a two step reductive amination procedure as illustrated below:

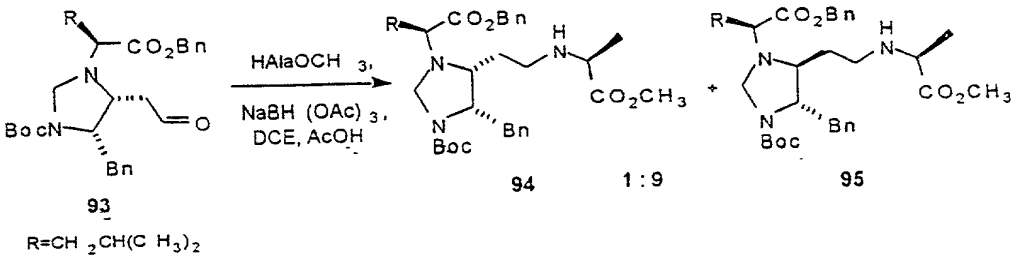


93 imine not isolated **94**

Alanine methyl ester hydrochloride (120 mg, 0.86 mmol) was dissolved in 1:1 brine:10%aq.Na_2CO_3 and extraction into CH_2Cl_2 (x2). The organic extracts were dried ($MgSO_4$), filtered and the majority of the solvent removed *in vacuo* to leave the volatile amine which was added to a solution of the freshly prepared aldehyde **93** (100 mg, 0.2 mmol) dissolved in methanol (~7 mL, strictly acid free). The solution was stirred at room temperature for 2 h whereupon analysis of a test portion reduced with $NaBH_4$ showed imine formation to be complete (none of the alcohol formed on reduction of aldehyde was detected). Solid $NaBH_4$ (50 mg, 1.3 mmol) was added to the solution and stirring continued for 10 min and then the reaction partitioned between ethyl acetate and a water/brine/10%aq.Na_2CO_3 mixture. The aqueous phase was separated and the organic layer washed with water (x2) then brine and then dried ($MgSO_4$). NMR analysis of the crude product failed to detect the corresponding trans (S) diastereomer (<5%). Evaporation of the solvent left an oil which was purified by flash chromatography eluting with 20-40% EtOAc in light petroleum for a 60-70% yield of **94**. TLC 40%EtOAc:light pet. Rf=0.43. Rotamers observed in the NMR spectra, ratio ~3:1, separate signals due to the minor rotamer recorded only where indicated. **^{1}H NMR** (300 MHz, CD_3CN, ref. 1.94 ppm): □ 7.37, 4H, m,; 7.3-7.1, 6H, m; 5.12, 5.09: 2H, ABq, J=12 Hz; 4.39 (major rotamer), 4.29 (minor): 1H, d, J=5 Hz; 4.15, 1H, J=5 Hz; 4.06, 1H, m, PheH□; 3.75-3.57, 4H, m, LeuH□+OCH_3; 3.25-3.10, 1H, m; 3.03, 1H, m; 2.87-2.60, 2H, m, Phe□; 2.52-2.25, 2H, m; 1.81, 1H, m; 1.67, 1H, m; 1.6-1.38, 2H, m; 1.34, bs, Boc minor rotamer; 1.19, m, Ala□; 1.15, bs, Boc major rotamer; 0.93, 3H, d, J=6.6 Hz; 0.89, 3H, d, J=6.3 Hz. **^{13}C NMR** (75 MHz, CD_3CN, ref. 118.69 ppm): □ 177.3; 173.4; 154.2; 141.0; 137.7; 131.2; 130.9; 129.9; 129.7; 129.6; 129.5; 127.1; 80.02 (Boc tertiary); 67.18 (CH_2); 62.55 (CH); 62.25 (CH_2); 60.75 (CH); 57.67 (2xCH, coincident signals); 52.55 (OCH_3); 45.96 (CH_2); 40.96 (CH_2); 36.15 (CH_2); 29.00 (Boc, minor rotamer); 28.73 (CH_2); 28.62 (Boc, major rotamer); 25.96 (CH);

23.66 (CH_3); 22.35 (CH_3); 19.7 (CH_3). Mass Spectrum (ISMS) m/z 596 ($M+H^+$), calculated for $C_{34}H_{50}N_3O_6$: 595.

Reductive amination of aldehyde **93** (or the 4,5-trans isomer) with $NaBH(OAc)_3$ in dichloroethane gave rise to a mixture of products **94** and **95** in the ratio 1:9.



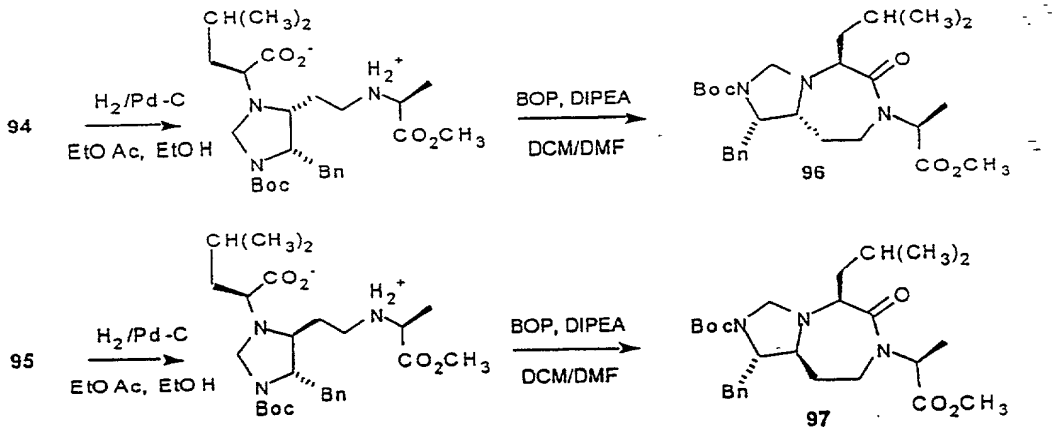
93

R=CH 2CH(C H3)2

The aldehyde **93** (50 mg, 0.1 mmol) was dissolved in 1,2-dichloroethane (5 mL) and alanine methyl ester (~2 equivalents) and acetic acid (1drop, ~14 mg) were added. The mixture was stirred at room temperature for 5 min and then $NaBH(OAc)_3$ (40 mg, 2 eq.) was added and stirring continued for 30 min. The solvent was then removed *in vacuo* and the residue partitioned between EtOAc and 10% aq. Na_2CO_3, the organic layer was washed with water and brine and then dried ($MgSO_4$). The product contained both diastereomers in the ratio ~9:1, trans:cis. The products were purified by flash chromatography eluting with 20-45% EtOAc in light petroleum. TLC 40% EtOAc:light pet. Rf=0.43 (minor diastereomer, **94**, cis), 0.23 (major diastereomer, **95**, trans). Combined yield ~60%. Rotamers were not observed although significant peak broadening was present, as observed for the corresponding trans aldehyde. The configuration of the major product was determined by NMR (NOESY experiment). **^{1}H NMR** (300 MHz, CD_3CN, ref 1.94 ppm): □ 7.24-7.14, 10H, m's; 5.13, 2H, s, OCH_2Ph; 4.38, 1H, br, ring methylene(i); 3.97, 1H, bd, ring methylene(ii); 3.61, 3H, s, OCH_3; 3.75, 1H, ddd, J=2.7, 4.3, 8.7 Hz, PheH□; 3.50, 1H, m, LeuH□; 3.13, 1H, m, PheC'H(ring); 2.97-2.88, 2H, m, AlaH□+PheH□(i); 2.72, 1H, dd, J=2.9, 8.7 Hz, PheH□(ii); 2.33, 1H, ddd, J=11.5, 7.3, 5.5 Hz, CH_2NH(bridge)(i);

1.98, 1H, m (dt, overlaps with solvent peak), CH_2NH(bridge)(ii); 1.53, 2H, m, Leu□+□; 1.43, 9H(s)+1H(m), Boc+Leu□; 1.35, 1H, m, bridge CH_2(i); 1.29, 1H, m, bridge CH_2(ii); 1.06, 3H, d, J=7.0 Hz, Ala□; 0.88, 6H, m, Leu□. **^{13}C NMR** (75 MHz, CD_3CN, ref 118.69 ppm): □ 177.2; 174.6; 154.5; 140.1; 137.6; 131.0; 129.9; 129.7; 129.6; 127.6; 80.61 (Boc tertiary); 67.50 (CH_2); 63.62 (CH_2); 63.5 (CH, br); 62.4 (CH, v.br); 60.67 (CH); 57.70 (CH); 52.47 (CH_2); 45.15 (CH_2); 40.65 (CH_2, v.br); 39.76 (CH_2); 32.81 (CH_2); 29.00 (CH_3, Boc); 26.21 (CH); 23.47 (CH_3); 22.88 (CH_3); 19.62 (CH_3). Mass Spectrum (ISMS) m/z 596 (MH^+), calculated for $C_{34}H_{49}N_3O_6$: 595.

The diastereomeric amines were converted to the protected □-turn mimetic compounds **96** and **97** as described below:



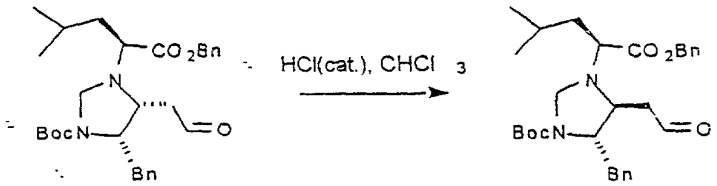
The 4,5-cis amine **94** (42 mg, 0.07 mmol) was dissolved in ethyl acetate:ethanol 10:3 (13 mL) and 35 mg of 10% palladium on activated carbon was added and the mixture hydrogenated at 32 psi H_2 for 3 h to deprotect the benzyl ester to the amino acid (MH^+ = 506 Da). The solution was filtered and the solvent removed *in vacuo*, then the residue was dissolved in DMF (2 mL) and diluted with CH_2Cl_2 (15 mL) and DIEA (50 mg, ~0.4 mmol) and BOP reagent (50 mg, 0.11 mmol) were added to the stirred solution at room temperature. The cyclisation was complete within a few minutes; the CH_2Cl_2 was then removed *in vacuo*

and the residue diluted with ethyl acetate and washed in turn with 10% aq.Na_2CO_3/brine, water (x2), brine and then dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a clear oil which was purified by flash chromatography eluting with 20% EtOAc in light petroleum for a yield of 25 mg (70%) of **96**. TLC 1:1 EtOAc:light pet ~0.45 The NMR spectra in CD_3CN at room temperature were significantly broadened indicating a degree of conformational interconversion slow on the NMR timescale. **^{1}H NMR** (300 MHz, CD_3CN): □ 7.32-7.15, 5H, m, Ar; 4.88, 1H, q, J=7.1 Hz, Ala□; 4.20, 1H, bd, J=4.8 Hz, NCH_2N(a); 4.13, 1H, m, Phe□; 4.09, 1H, bd, J=5.0 Hz, NCH_2N(b); 3.72, 1H, m, Leu□; 3.65, 3H, s, OCH_3; 3.52, 1H, bdd, J=10.6, 15.2 Hz, bridge CH_2CH_2N(a); 3.30-3.21, 2H, m's CH_2CH_2N(b) and PheC'H; 2.94, 1H, bm, Phe□(a); 2.76, 1H bm Phe□(b); 2.25 water peak; 1.9-1.4, 5H, e, Leu□+□ and bridge CH_2CH_2N; 1.29, 3H, d, J=7.1 Hz, Ala□; 3.25, 9H, vbr, Boc; 0.92, 6H, d, J=6.2 Hz, Leu□. **^{13}C NMR** (75 MHz, CD_3CN): □ 173.5 (the amide and ester peaks appear to be co-incident); 154.9 (carbamate, br); 140.7; 130.7 (br); 129.6; 127.3; 80.54; 66.47; 63.83 (br); 62.36; 60.4 (very br); 56.29; 52.97; 44.77; (36.96, 36.40) very br, just resolved; 33.3 (very br); 28.78 (Boc, br); 26.86; 23.90 (br); 22.63; 15.47. Mass spectrum (ISMS) m/z 250.2 ($M+H^+$), calculated for $C_{28}H_{37}N_3O_6$: 511 fragments (OR 60): 441, (-tBu); 397, (-Boc).

The synthesis of **97** was as for **96** but using the trans amine **95**. TLC 1:1 EtOAc:light pet. Rf=0.53. The NMR spectra in CD_3CN were were well resolved and rotamers were present in the ratio of 11:9; signals attributable to the same atom in the different rotamers are placed in parentheses where possible. **^{1}H NMR** (300 MHz, CD_3CN, ref 1.94 ppm): □ 7.34-7.16, 5H, m; 4.69, 1H, m; 4.13, 1H, d, J=4.4 Hz; 3.92, 1H, m; (3.83, d, J=4.4; 3.79, d, J=4.4 Hz), 1H; 3.76-3.60, 2H, m's; (3.61, s; 3.81, s), 3H, OCH_3; 3.26, 1H, m; 3.15, 1H, m; 2.99, 1H, m; 2.77, 1H, m; 1.85-1.49, 3H, m's; (1.44, s; 1.41, s), 9H, Boc; 1.30, 3H, d, J=7.2 Hz, Ala□; 1.36-1.24, 2H, m; 0.98-0.91, 6H, m. **^{13}C NMR** (75 MHz, CD_3CN, ref 118.69 ppm): □ 174.4; 173.3; 154.6; (140.54, 140.49); 130.7;

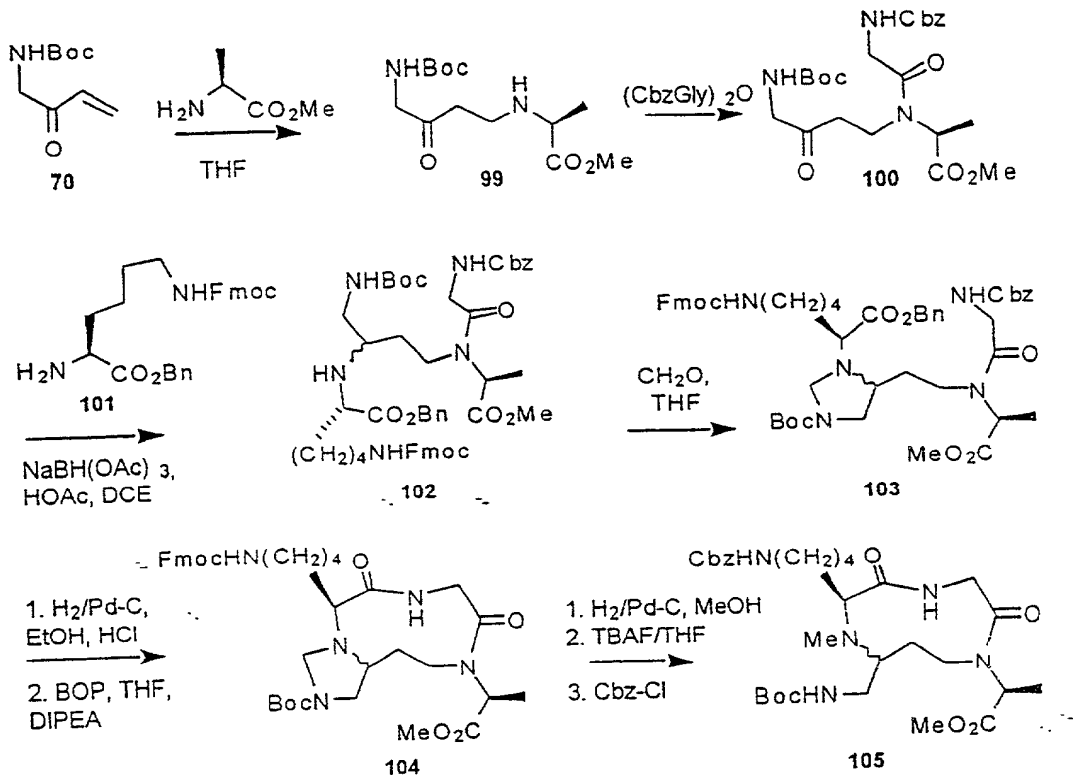
130.6; 129.8; 127.6; (80.65, 80.54), Boc tertiary; (66.12, 65.48, 65.21, 64.90) 2xCH; 60.67, CH_2; (56.82, 56.74), CH; (56.41, 56.24), CH; 52.87, CH_3; (46.19, 46.12), CH_2; (40.72, 39.84), CH_2; 39.16, CH_2; 30.44, CH_2; (29.03, 28.93) Boc; (25.64, 25.58), CH; 24.19, CH_3; 22.43, CH_3; 15.76, CH_3. Mass Spectrum (ISMS) m/z 488 (MH^+), calculated for $C_{28}H_{37}N_3O_6$: 487.

Example (G). *Acid catalysed isomerisation of aldehydes **93***



The trans (4(S)) aldehyde was obtained by the acid catalysed isomerisation of the cis diastereomer **93** in chloroform solution with catalytic HCl present. Significant decomposition to multiple unidentified by-products (most having high Rf) also occurs under the isomerisation conditions. The product was purified by flash chromatography eluting with 15% ethyl acetate in petroleum ether for a yield of about 35% **98** from crude **93**. **^{1}H NMR** (300 MHz, CD_3CN, ref. 1.94 ppm): □ 9.41, t, J=1.8 Hz; 7.45-7.10, 10H, m; 5.12, 2H, m, OCH_2Ph; 4.46, 1H, br; 4.01, 1H, bd; 3.82, 1H, m; 3.62-3.46, 2H, m; 2.95, 1H, bdd, J=13.0, 4.4 Hz; 2.81, 1H, dd, J=13.2, 8.0 Hz; 2.37, 2H, m (ABq of dd, J_{AB}=31, J_{ddA}=4.6, 1.8 Hz; J_{ddB}=7.2, 2.1 Hz), □-aldehyde; 1.75-1.25, 12H, e (1.4, bs, Boc); 0.9, 6H, bm. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 202.9; 174.5; 154.4; 139.7; 137.5; 131.0; 129.9; 129.8; 129.7; 127.7; 80.81; 67.61; 64.03 (br); 63.18 60.49; 59.9 (br); 47.0 (br); 45.95; 39.88; 28.96 (Boc); 26.12; 23.25; 22.97.

Example (H). *Synthesis of a □-turn mimetic **II(i)***



Compound **70** was prepared as described above, and reacted with alanine methyl ester to form **99** using the same method previously described for the synthesis of **71**. The crude amino ketone **99** (1.22g) was reacted with Cbz-glycine symmetric anhydride (synthesised from 1.95g CbzGlyOH and 9.3mls 0.5M dicyclohexylcarbodiimide in dichloromethane) and 0.6g DIEA in dichloromethane. The reaction was stirred at room temperature for 10 hours then diluted with ether (any DCU precipitate was filtered off) and the ether solution was washed with 1M HCl, aqueous sodium bicarbonate then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with 2:1 ethyl acetate:light petroleum ether, yield of **100** was 1.8g (90%). Reductive amination of **100** with **101** derived from the deprotection of BocLys(Fmoc)OBn (TFA, CH_2Cl_2) is carried out by the previously described method for the formation of **73** (71% yield after flash chromatography eluting with 2:1 to

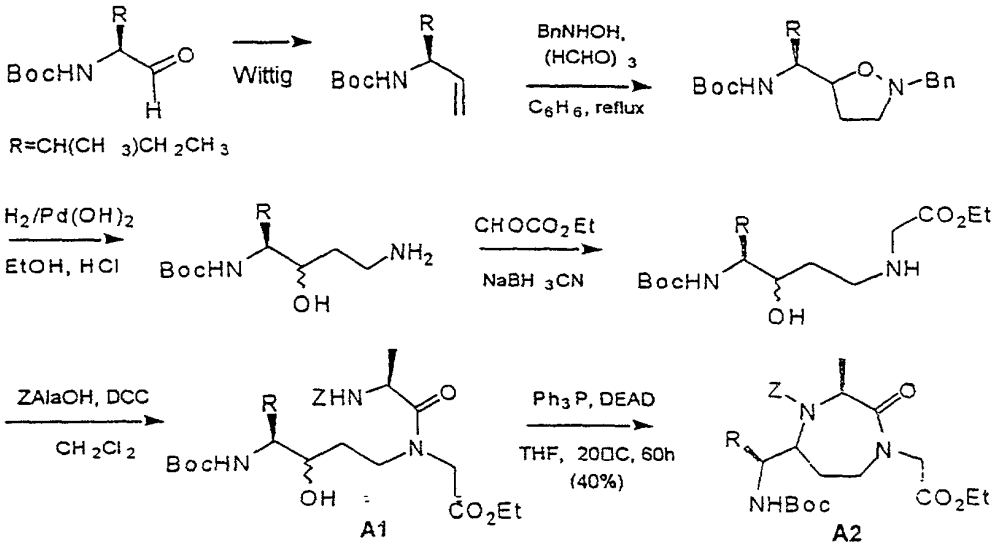
3:1 ethyl acetate:light petroleum). The product amine **102** was dissolved in ethyl acetate and formalin added to the stirred solution resulting in the formation of imidazolidine **103**. The ethyl acetate solution was washed with aqueous sodium bicarbonate, water (twice), brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with 3:2 ethyl acetate:light petroleum ether (yield >75%). The protected pre-cyclisation compound **103** (400 mgs) was dissolved in 0.1M ethanolic HCl (20 mls) and hydrogenated with 250mgs of 10% Pd-C. The hydrogenation was complete after 7 hours (about 40 psi H_2, room temperature). The solution was filtered through a celite pad to remove the catalyst and 50 mls of DMF added. Volatiles (ethanol) were removed under reduced pressure then a solution of BOP reagent (300 mgs) and DIEA (300 mgs) in 150 mls of DMF was added and the mixture stirred at room temperature for 15 minutes. Most of the DMF was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with 1M HCl, aqueous sodium bicarbonate, water (twice), brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave about 300 mgs of crude product **104**. The crude product was dissolved in 30 mls methanolic HCl (0.1M) and hydrogenated (200mgs Pd-C, 40psi H_2) for 24 hours reducing the imidazolidine to an N-methyl group. The catalyst was filtered off (celite) and the solvent removed under reduced pressure, the residue was then treated with tetrabutylammonium fluoride in THF to remove the FMOC group. The free amine was then reprotected by addition of benzyl chloroformate (65 mgs) and DIEA (100 mgs). After stirring for 1 hour ethyl acetate was added and the organic layer was washed with 1M HCl, water, then brine, dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave an oil which was purified by flash chromatography eluting with 3-5% ethanol in chloroform for a yield of about 40% of **105** based on **103**.

APPENDIX

Previous reports of the □-turn mimetic system **I(i)**

A theoretical study of the suitability of various heterocyclic systems as □-turn mimetics has been published (Alkorta *et al.*, 1996). The study included the 1,3,5-substituted-1,4-diaza-2-oxocycloheptane system (the basis of the □-turn mimetics described herein). No synthesis was described or referenced in the paper for this mimetic system, in contrast to other known mimetic systems where the synthesis was referenced.

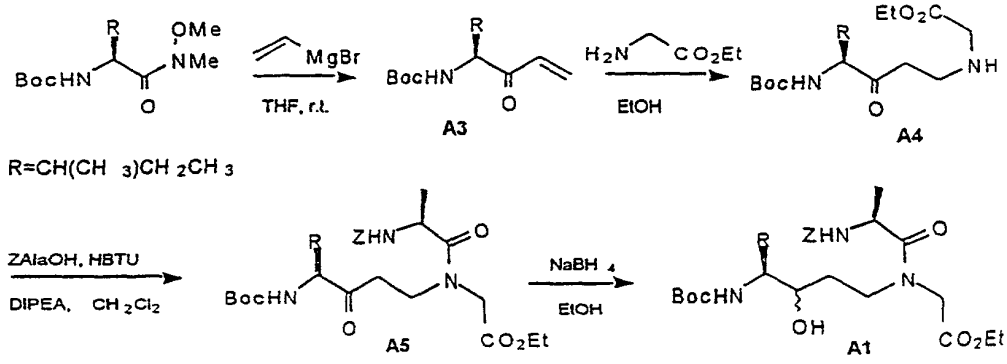
Although a search of the Chemical Abstracts registry file on the substructure of the □-turn system gave only the above modelling study, we are aware of a reported synthesis of the □-turn mimetic system by a different synthetic approach. The alternative approach was described in a poster presented at the 23rd European Peptide Symposium (1994), and repeated at the end of a review published in the Bulletin of the Chemical Society of Belgium (Guilbourdenche *et al.*, 1994) and again the following year (Ma *et al.*, 1995). Our research and other literature results do not support this alternative method, the reports are in error and do not represent a reduction to practice. We have repeated the cyclisation reaction described by Ma *et al.*, 1995 and confirmed by NMR analysis and chemical transformation that the actual product is a structural isomer, not the □-turn mimetic claimed. The synthesis and analyses and other material in support of the assertion that the method of Ma et al. does not represent a reduction to practice are presented below.



Scheme A1 Synthesis proposed by Ma *et al.*, 1995 for a 1,4-diazepine □-turn mimetic.

The key step in the proposed synthesis of Ma *et al.*, 1995 is the cyclisation of **A1** to the protected target **A2** using the Mitsunobu reagents. We repeated the synthesis of the cyclisation precursor by our own methods as described below.

The alcohol **A1** was more conveniently prepared by the conjugate addition method described earlier than as illustrated in Scheme A1 (4 steps vs. 6 steps). The procedure used is summarised in Scheme A2.



Scheme A2

Thus the Weinreb amide of Boc isoleucine was reacted with vinyl Grignard in THF to give the □-□ unsaturated ketone **A3** by the following procedure: Boc-isoleucine-N-methoxy-N-methylamide (2.25 g, 8.2 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0°C under nitrogen. To the stirred solution was added vinyl magnesium bromide in THF (20 mL of a ~1M solution) over 5 min. The reaction was very slow at 0°C (negligible progress over 1 h), but much faster at room temperature (~70% product after 20 min). After stirring at room temperature for 90 min the reaction was poured into crushed ice/1M HCl and extracted with ether. The organic layer was washed with 0.5M HCl, water, aq.$NaHCO_3$ then brine and then dried over $MgSO_4$. The crude product was formed in good yield and purity and was used directly for the next reaction. TLC 25%EA/light pet. Rf=0.64. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 6.50, 1H, dd, J = 10, 17 Hz; 6.37, 1H, dd, J = 1, 17 Hz; 5.85, 1H, d, J = 10 Hz; 5.23, 1H, bd, J = 7 Hz; 4.58, 1H, dd, J = 4, 8 Hz; 1.88, 1H, m; 1.45, 9H, s; 1.32, 1H, m; 1.10, 1H, m; 0.98, 3H, d, J = 7 Hz; 0.90, 3H, d, J = 7 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 199.0; 155.7; 134.0; 129.6; 79.60; 61.71; 37.50; 28.28 (Boc); 24.09; 16.04; 11.61.

Reaction of **A3** with glycine ethyl ester in ethanol to give **A4** by the following procedure: Glycine ethyl ester hydrochloride (1.0 g, 7.1 mmol) was reacted with **A3** (1.1 g, ~4.7 mmol) and DIEA (450 mg, 3.5 mmol) in ethanol (20 mL) at room temperature overnight. The reaction was diluted with ether (100 mL) and extracted in turn with aq. $NaHCO_3$ and water (x3). Petroleum ether was added (100 mL) and the solution extracted with 0.5M HCl:MeOH 4:1 (x3) (discard the organic layer). The acid washings were immediately neutralised with solid $NaHCO_3$ and then extracted with ethyl acetate and the ethyl acetate layer washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* left 800 mg (~50%) of crude product of sufficient purity for use in the next reaction. TLC EtOAc Rf=0.52. **^{13}C NMR** (75 MHz, $CDCl_3$): □ 209.0; 171.7; 155.8; 79.57; 63.95; 60.76; 50.67; 43.69; 40.82;

36.74; 28.19 (Boc); 24.05; 16.01; 14.08; 11.51. Mass Spectrum (ISMS) m/z 345 (MH^+), calculated for $C_{17}H_{32}N_2O_5$: 344.

The amino ketone **A4** (690 mg, 2 mmol) was then coupled with Z-alanine to give **A5** using standard solution phase coupling procedure with HBTU reagent and DIEA in CH_2Cl_2/THF. The crude product was purified by flash chromatography eluting with 30% EtOAc in light petroleum for a yield of 94% (1.03 g). TLC EtOAc:light pet. 1:2 Rf=0.25. **^{1}H NMR** (300 MHz, $CDCl_3$): □ 7.34, 5H, m; 5.68, 1H, bm; 5.18-5.02, 3H, m's; 4.72, 0.5H, m; 4.48-4.07, 5H, m's; 3.88-3.54, 2.5H, m's; 2.75-2.05, 2H, m's; 1.89, 1H bs; 1.44, 1.43: 9H, 2s, Boc; 1.38, 1.5H, d, J= 6.9 Hz (alaH□, one rotamer); 1.34-1.28, 5.5H, m's; 1.07, 1H, m; 1.00-0.82, 6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), signals due to the equivalent carbon in different rotamers are grouped in parentheses where possible: □ (209.0, 207.9); (173.39, 173.25); (169.15, 168.84); 155.75, 155.67, 155.56, 155.33: carbamate signals; 136.20; 128.31; 127.91; 127.80; (79.72, 79.57); 66.60; (64.01, 63.85); (61.61, 61.09); (50.96, 48.65); (46.63, 46.57); (43.75, 43.23); (40.02, 39.07); (36.56, 36.29); 28.14 (Boc); (24.09, 24.03); 18.74; 15.92; 13.85; (11.44, 11.38). Mass Spectrum (ISMS) m/z 550 (MH^+), calculated for $C_{28}H_{43}N_3O_8$: 549

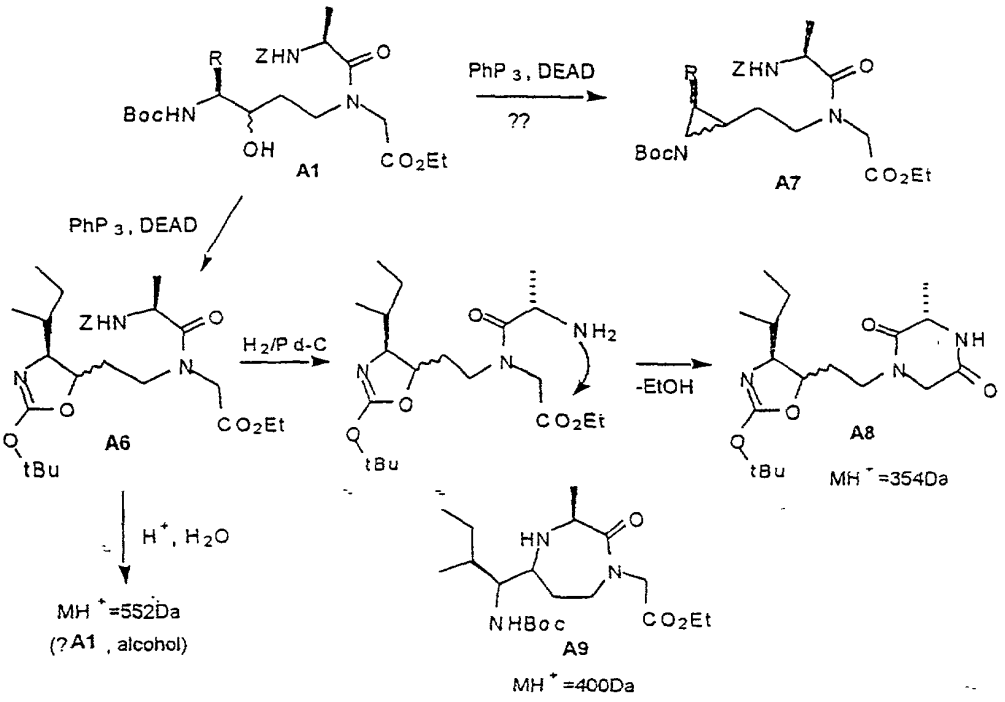
The ketone **A5** (430 mg, 0.78 mmol) was dissolved in ethanol (5 mL) and $NaBH_4$ (15 mg, 0.40 mmol) added to the stirred solution at room temperature, and stirring continued for 1 h. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and washed with 1M HCl, water, aq. $NaHCO_3$, brine and then dried over $MgSO_4$. The residue after solvent evaporation was purified by flash chromatography eluting with ethyl acetate:light petroleum ~1:1 (some separation of diastereomers occurred) for an approximately quantitative yield of the alcohol **A1**. TLC EtOAc:light pet. 1:1 Rf=0.28. **^{1}H NMR** (300 MHz, $CDCl_3$), late eluting fractions, rotamers/diastereomers >2:1: □ 7.39-7.29, 5H, m; 5.80, 1H, d, J=9 Hz; 5.15, 1H, d, J=12 Hz; 5.11-5.49, ~1H, m; 4.96, ~1H, d, J=12 Hz; 4.67-4.42, ~1H, m's; 4.19, ~2H, bq, J=7.2 Hz; 4.03-3.88, ~2H, bm; 3.88-3.40, ~4H, m's; 3.30-3.09, 1H, m; 1.96-1.66,

~2H, m; 1.55, ~1H, m; 1.42, 9H, s, (Boc); 1.331.33, d, J=7 Hz; 1.28, t, J=7.2 Hz; 1.15, d (minor isomer), J=6.8 Hz; 1.37-1.05 ~8H; 1.0-0.82, ~6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), major peak only shown unless otherwise indicated: □ 174.0; 169.0; 156.4; 156.3; 135.9; 128.4; 128.1; (128.0, minor isomer); 127.9; 78.92; 66.96; (66.56, minor isomer); 66.11; 61.26; 59.49; 47.74; 46.10; 45.24; 34.38; 31.31; 28.30 (Boc); 22.29; 18.85; 16.41; 14.00; 11.90. Mass Spectrum (ISMS) m/z 552 ($M+H^+$), calculated for $C_{28}H_{45}N_3O_8$: 551.

The alcohol **A1** was reacted with the Mitsunobu reagents as described by Ma *et al.*, 1995 (Scheme 4.37) as follows: The alcohol **A1** (150 mg, early eluting fraction) was dissolved in dry THF and triphenylphosphine (71 mg) added. To the stirred solution at room temperature under nitrogen was added DEAD (43 uL), and stirring continued for 24 h. Analysis of the crude reaction revealed the formation of a dehydration product ($M+H^+$=534 Da) in moderate yield. Another equivalent of triphenylphosphine/DEAD was added and stirring continued for a further 48 h. The solvent was removed *in vacuo* and the residual oil dissolved in ether/petroleum ether and left to stand to encourage the precipitation of the triphenylphosphine oxide and diethoxycarbonyl hydrazine (white solid, filtered off). The oil remaining after evaporation of the filtrate was purified by flash chromatography eluting with petroleum ether and 10-100% ether in petroleum ether, yield was ~40% (60 mg). TLC ethyl ether Rf=0.61. The NMR spectra were quite complex, as may be expected from the possible mixture of diastereomers/ rotamers. However, it was possible to clearly identify the alanine spin system with H□ at 4.71 ppm (1H, broad pentuplet, J~8Hz). 1D decoupling experiments were performed: irradiation at 4.7 ppm caused the collapse of two signals to singlets, a doublet centred on 1.40 ppm (J=7Hz, alanine H□), and a broad doublet (1H, J=8Hz) at 5.62ppm (alanine NH). These assignments were confirmed by irradiation at 1.4 ppm which caused collapse of the multiplet at 4.71 ppm to a doublet with J=8Hz. The presence of the NH proton in the alanine spin system rules out the □-turn

mimetic **A2** proposed by Ma *et al.*, 1995 as a possible structure for the product, and leaves open the possibility of **A6** or **A7** (Scheme A3) which we felt were more probable products, as the true structure. **^{1}H NMR** (300 MHz, $CDCl_3$): (selected peaks) □ 5.62, ~1H, bd, J=8 Hz; 4.71, ~1H, m(q); 1.40, d, J=6.8 Hz. Decoupling experiments: irradiate 1.4 ppm -> 4.71 = doublet, J=8 Hz; irradiate 4.71 ppm -> 1.4 = singlet, 5.62 = singlet. **^{13}C NMR** (75 MHz, $CDCl_3$): the spectra were difficult to analyse due to the presence of rotamers/diastereomers, peak broadening and impurities which co-eluted. There were a couple of notable features: (i) the appearance of a new peak at the relatively unusual shift of 160.7 ppm possibly due to the carbamate derived oxazoline carbon (only one carbamate resonance was observed, 155.5 ppm), and (ii) the downfield shift of the tertiary Boc carbon resonance which was observed at 81.22 ppm, whereas NHBoc tertiary carbon shifts are normally at a shift upfield of 80 ppm (e.g. 78.9 in the alcohol precursor). Mass Spectrum (ISMS) m/z 534 (MH^+), calculated for $C_{28}H_{43}N_3O_7$: 533.

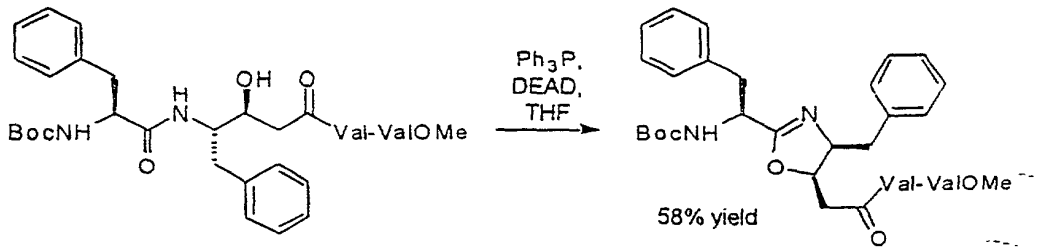
To confirm the results of the NMR analysis a further experiment was carried out. The product material was hydrogenated (EtOH, Pd-C) to remove the Z group. If the product has structure **A6** or **A7** then the amine will now be free to form the diketopiperazine **A8**, a facile reaction in such a system, Scheme A3. If any of the target □-turn mimetic **A2** is present then it will be deprotected to the (very stable) free amine **A9** and be easily detected in the ionspray mass spectrum (ISMS). Analysis of the product mixture from the hydrogenation revealed the presence of a mass peak corresponding to the diketopiperazine (MH^+=354Da), but no trace whatsoever of **A9** (MH^+=400Da).



Scheme A3

Finally, it was also observed that the cyclisation product (which we propose to be **A6**) was easily hydrolysed by dilute aqueous acid (e.g. room temperature 0.1% aq. TFA, 12 h), back to the alcohol **A1** (or a compound of the same mass). This last observation is more consistent with the product structure being the oxazoline **A6** rather than the aziridine **A7** as the oxazoline is more probably subject to facile hydrolysis by aqueous acid, the facile hydrolysis is entirely inconsistent with the structure **A2** proposed by Ma *et al.*, 1995

In further support of **A6** as the product structure, peptide alcohols similar in structure to **A1** have been reported to form oxazolines, (Galéotti *et al.*, 1992) for example:



Other evidence against formation of **A2** by the Mitsunobu reaction as proposed by Ma *et al.*, 1995 is presented below.

(1) Difficulty of forming seven membered rings via the Mitsunobu reaction

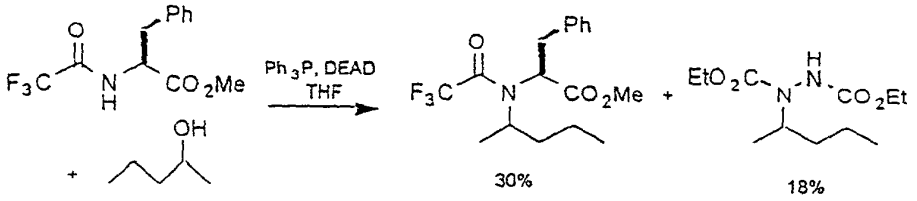
(a) Literature precedent

The literature on the formation of cyclic amines and amides with the Mitsunobu reaction contains numerous examples of the formation of 3-6 membered rings (Carlock and Mack, 1978; Robinson *et al.*.1983; Pfister, 1984; Kelly *et al.*, 1986; Henry *et al.*, 1989; Bernotas and Cube, 1991), but very few cases of seven membered ring formation. In one paper on the cyclisation of amino alcohols the faliure to form a simple seven membered target is specifically described (Bernotas and Cube, 1991) In the organic reactions entry on the Mitsunobu reaction (Hughes, 1992) three instances of seven membered ring formation with carbon-nitrogen bond formation are described: all three involve a primary alcohol, two occur in polycyclic systems and appear to be special cases, and the third involves alkylation of a hydroxamide - far easier than an amide due to higher NH acidity.

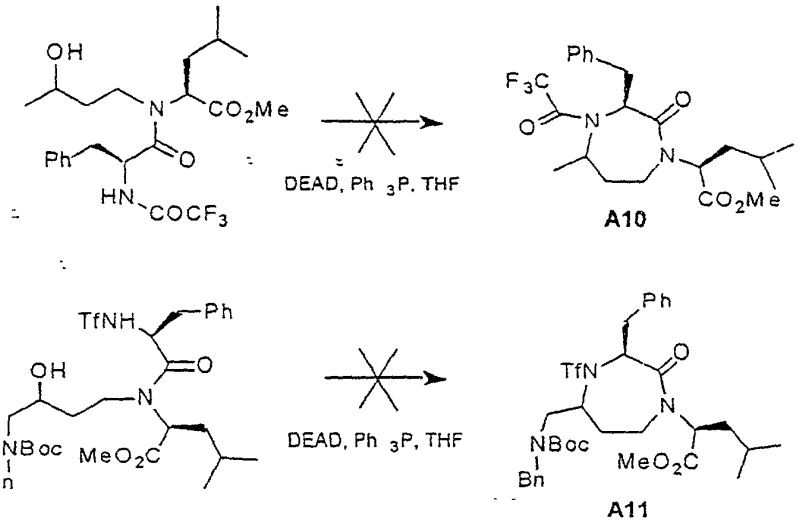
There appears to be no literature precedent for the formation of a seven membered ring to a simple amide or carbamate nitrogen. In addition there is little precedent for secondary amide N-alkylation with hindered secondary alcohols, as is proposed to occur in the formation of **A2**.

(b) Synthetic studies

Extensive studies on the use of the Mitsunobu reaction for the formation of the target system were carried out in our laboratories prior to becoming aware of the proposed synthesis. In our hands this approach was ineffective. The key reactions are described in Schemes A4 and A5.



Scheme A4

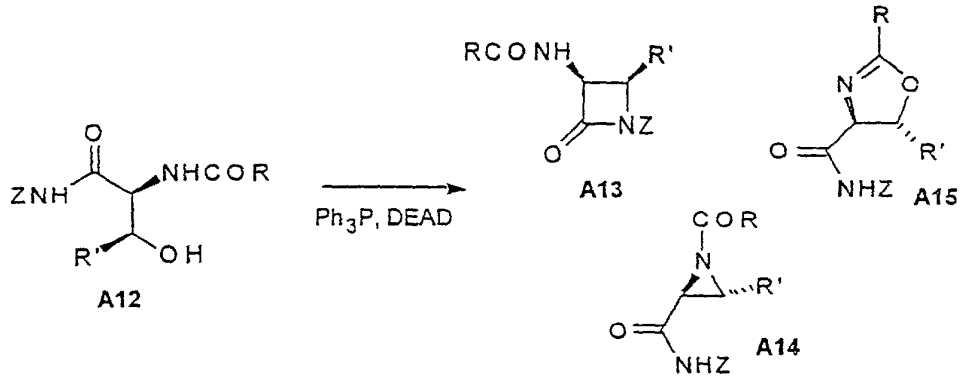


Scheme A5

The formation of the alkylation product was somewhat successful in the intermolecular reaction (Scheme A4), but this success was not repeated in cyclic systems (Scheme A5). No significant amount of the target cyclic products **A10** or **A11** was detected.

(2) ***<u>Competing reactions - oxazoline and aziridine formation</u>***

Cyclisation of □-hydroxy amide derivatives A12 with the aim of forming □-lactams **A13** also results in the formation of the aziridine **A14** and oxazoline **A15** products shown in Scheme A6 (Hughes, 1992). Another example of oxazoline formation was described above (Galéotti *et al.*, 1992).



Scheme A6

As the Mitsunobu reaction is relatively effective for the formation of small ring sizes, it is quite probable that the formation of aziridines and oxazolines will compete with other possible cyclisations, other factors being equal. Such competition can take place in the proposed synthesis, the products would then be **A6** and/or **A7**, Scheme A3. Both the aziridine and oxazoline are isomeric with the target compound **A2**, possibly leading to their confusion with the target, a situation easily resolved by ^{1}H NMR as we demonstrated above.

In summary, the proposed method is in error because:

- We have repeated the cyclisation and found the product to be a structural isomer of the target, probably the oxazoline **A6**.

This finding is supported by:-

- Literature contrindications (competing cyclisations favoured), lack of precedent (seven membered rings difficult to form by the Mitsunobu reaction).
- Extensive studies in our laboratories which indicate the Mitsunobu approach is generally ineffective for the synthesis of the □-turn mimetics.

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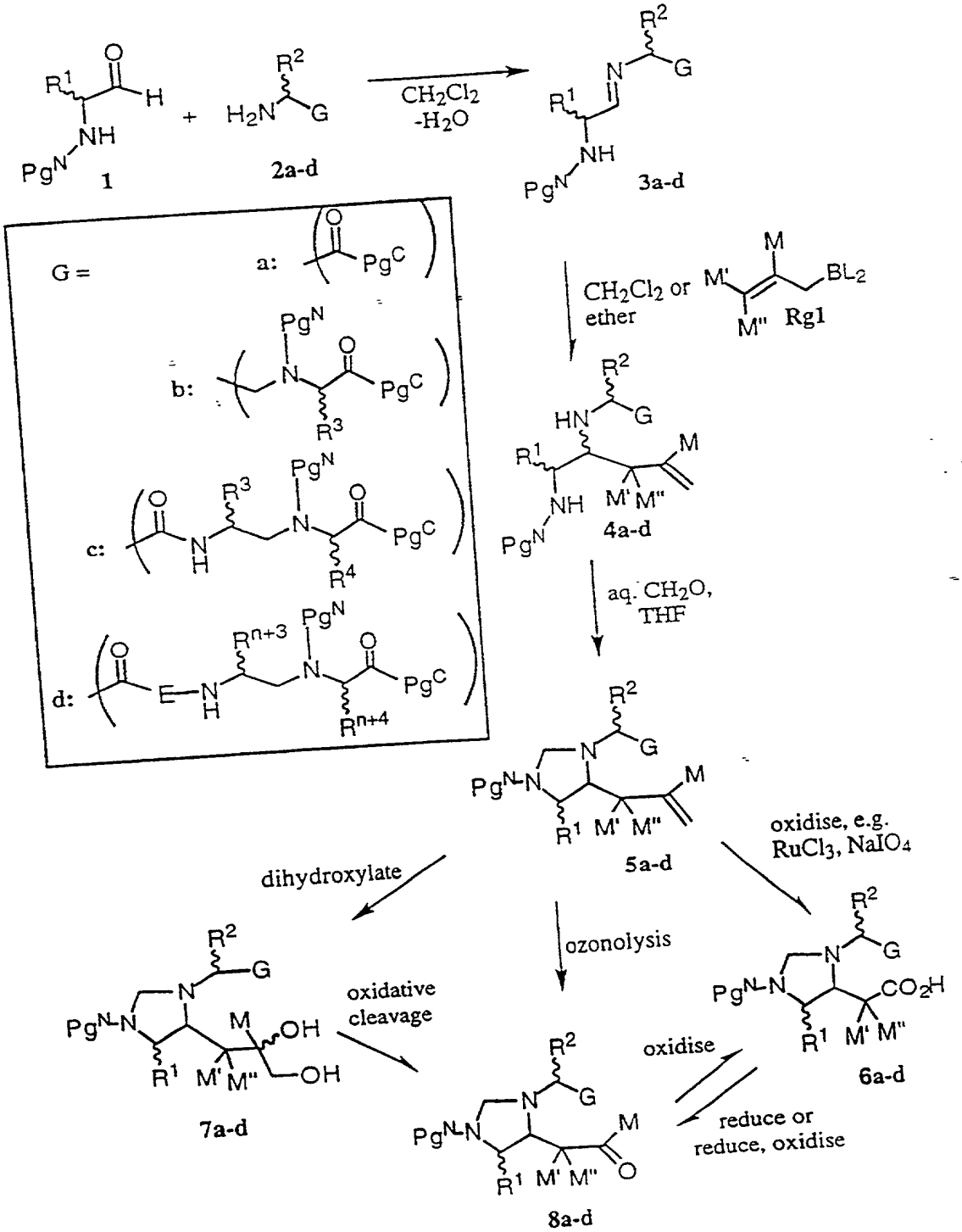
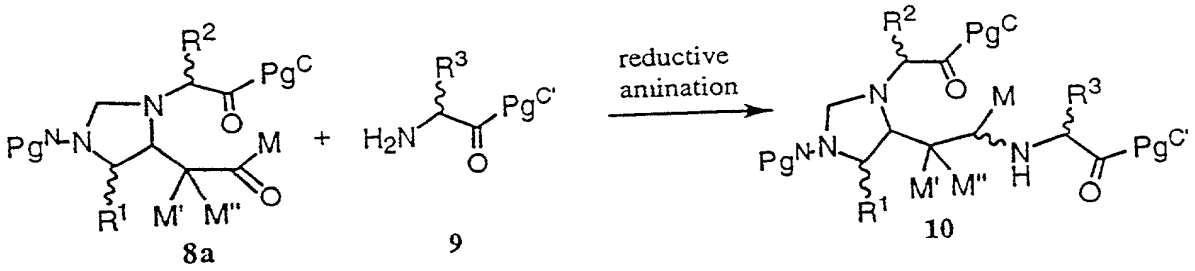
SCHEME 1

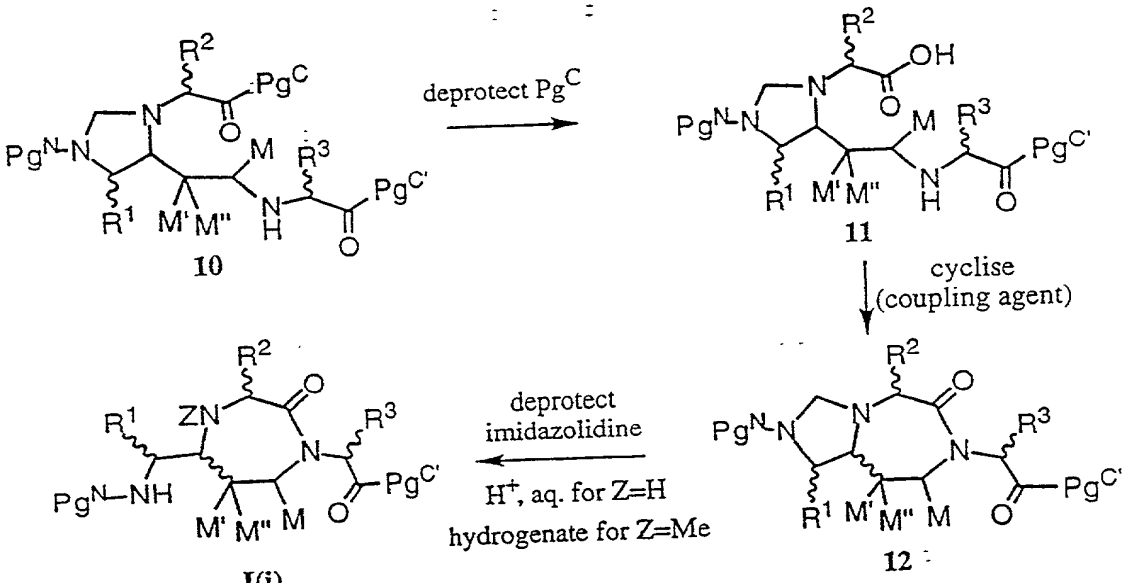


Scheme 1

SCHEMES 2 AND 3

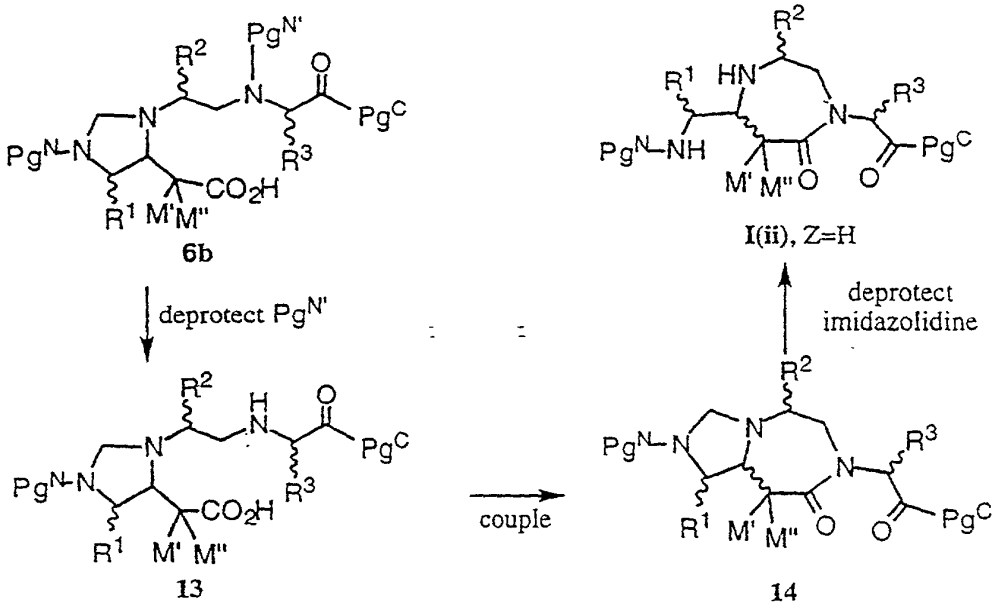


Scheme 2



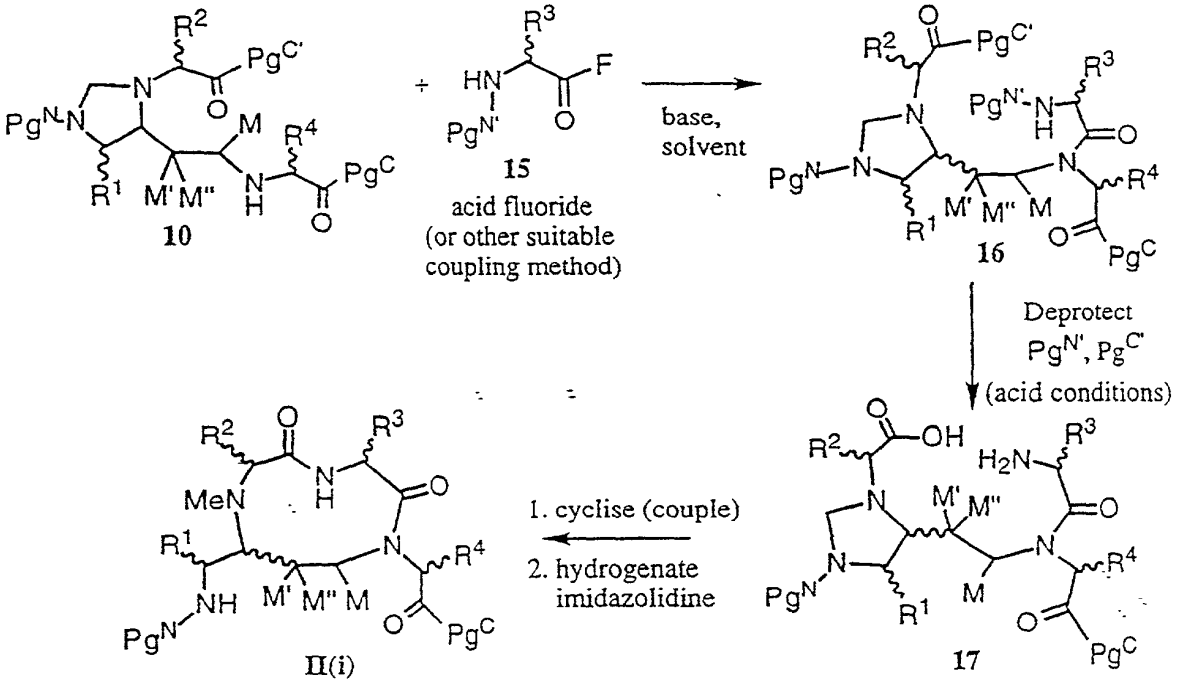
Scheme 3. Synthesis of γ-turn mimetics **I(i)**.

SCHEME 4

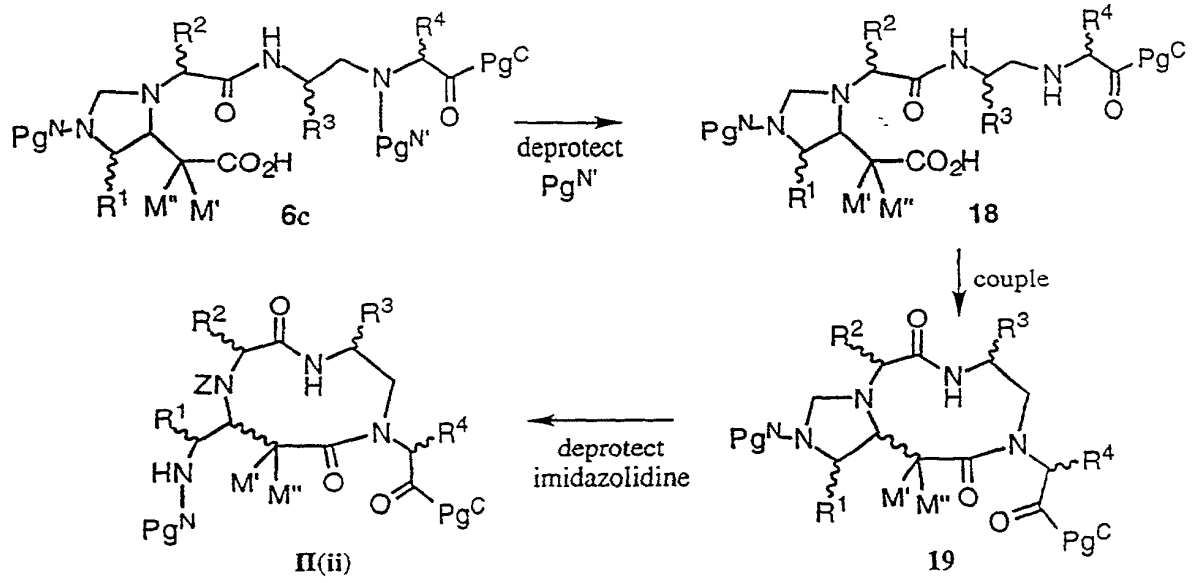


Scheme 4. Synthesis of γ-turn mimetics I(ii).

SCHEMES 5 AND 6

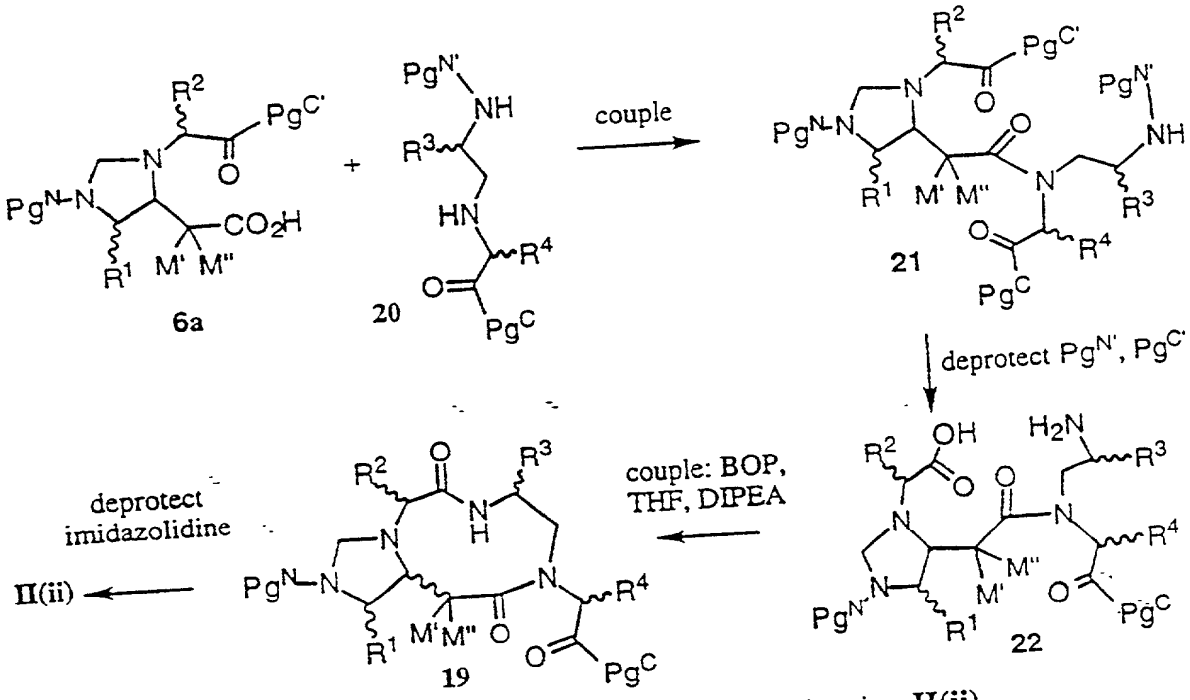


Scheme 5. Synthesis of of β-turn mimetics II(i).

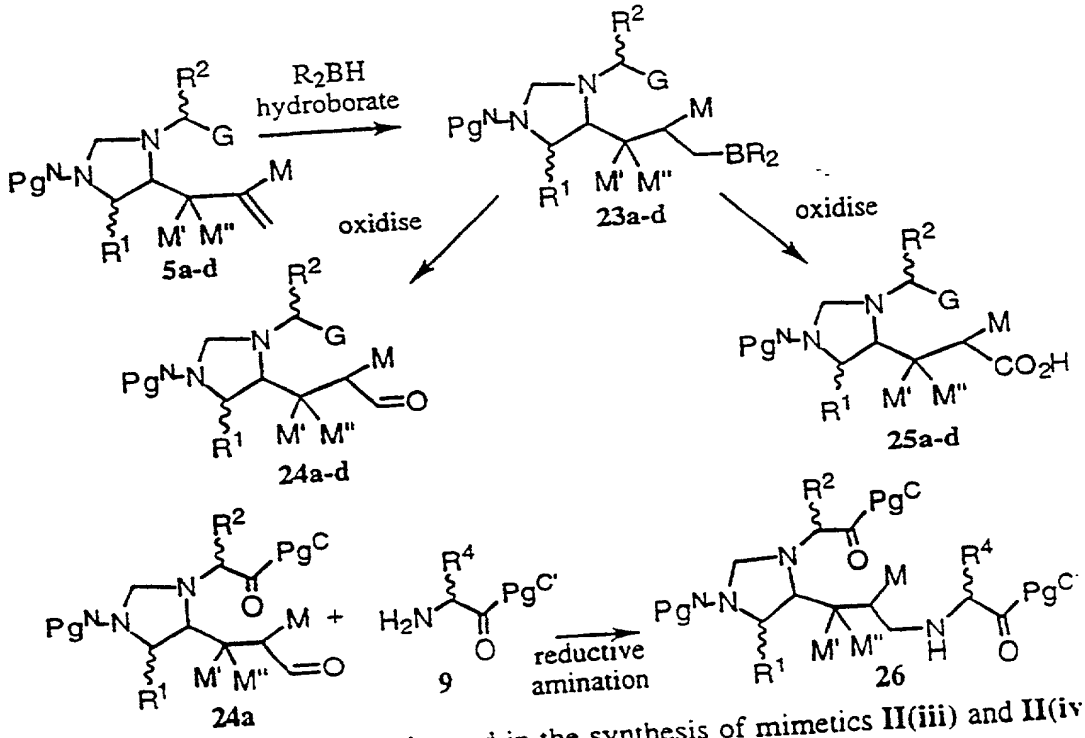


Scheme 6. Synthesis of β-turn mimetics II(ii).

SCHEMES 7 AND 8

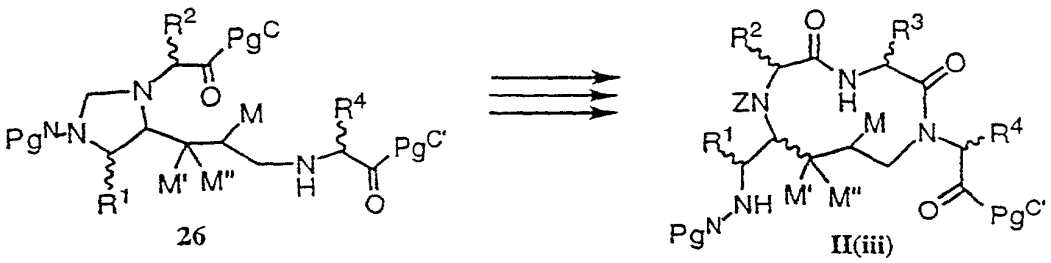


Scheme 7. Alternative synthesis of beta turn mimetics **II(ii)**

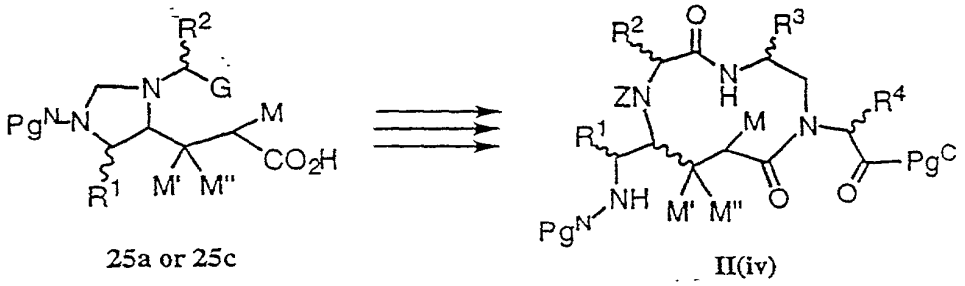


Scheme 8. General methods used in the synthesis of mimetics **II(iii)** and **II(iv)**

SCHEMES 9 AND 10

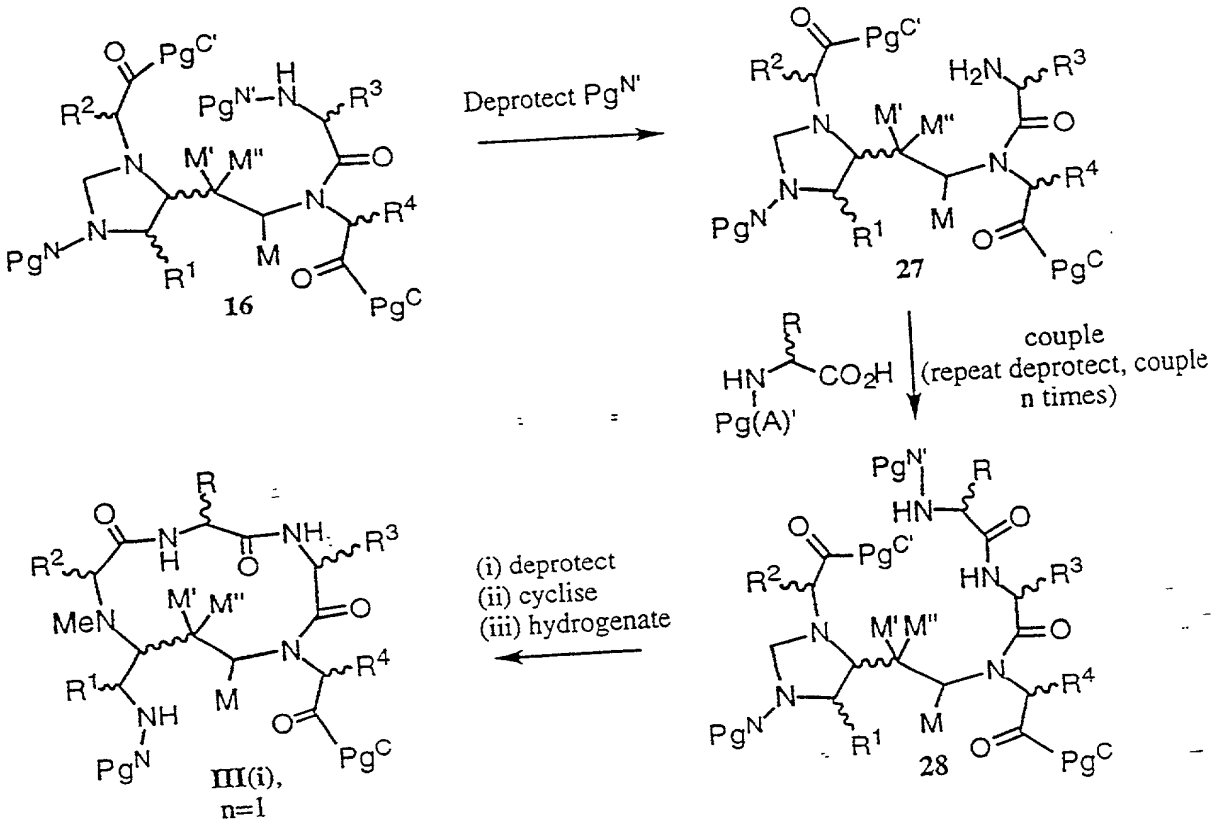


Scheme 9. Synthesis of beta turn mimetics **II(iii)**: Same method as described in Scheme 5, substituting **26** for **10**.



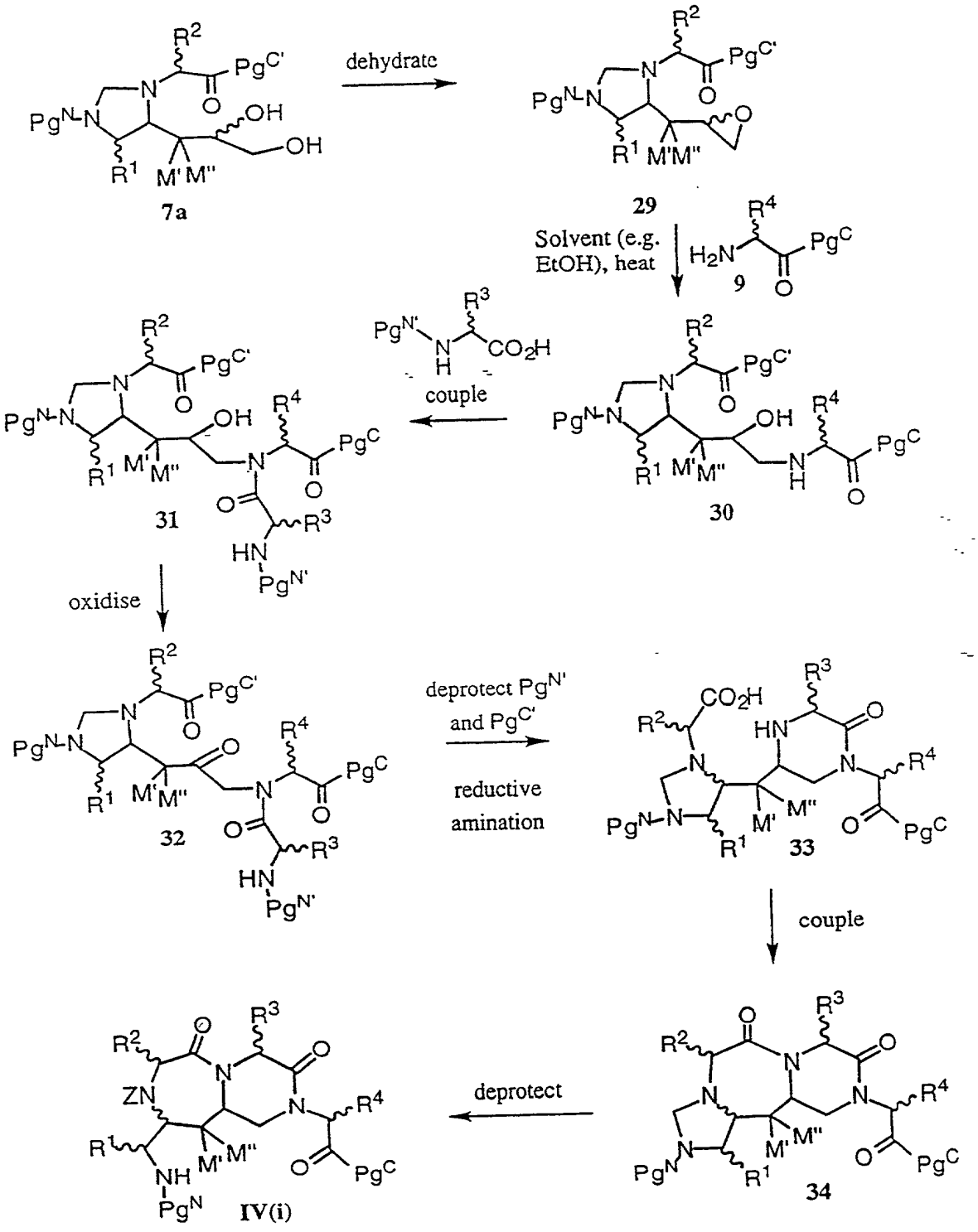
Scheme 10. Synthesis of beta turn mimetics **II(iv)**: same method as described in Scheme 6, substituting **25c** for 6c; alternatively, same method as for Scheme 7, substituting **25a** for **6a**.

SCHEME 11



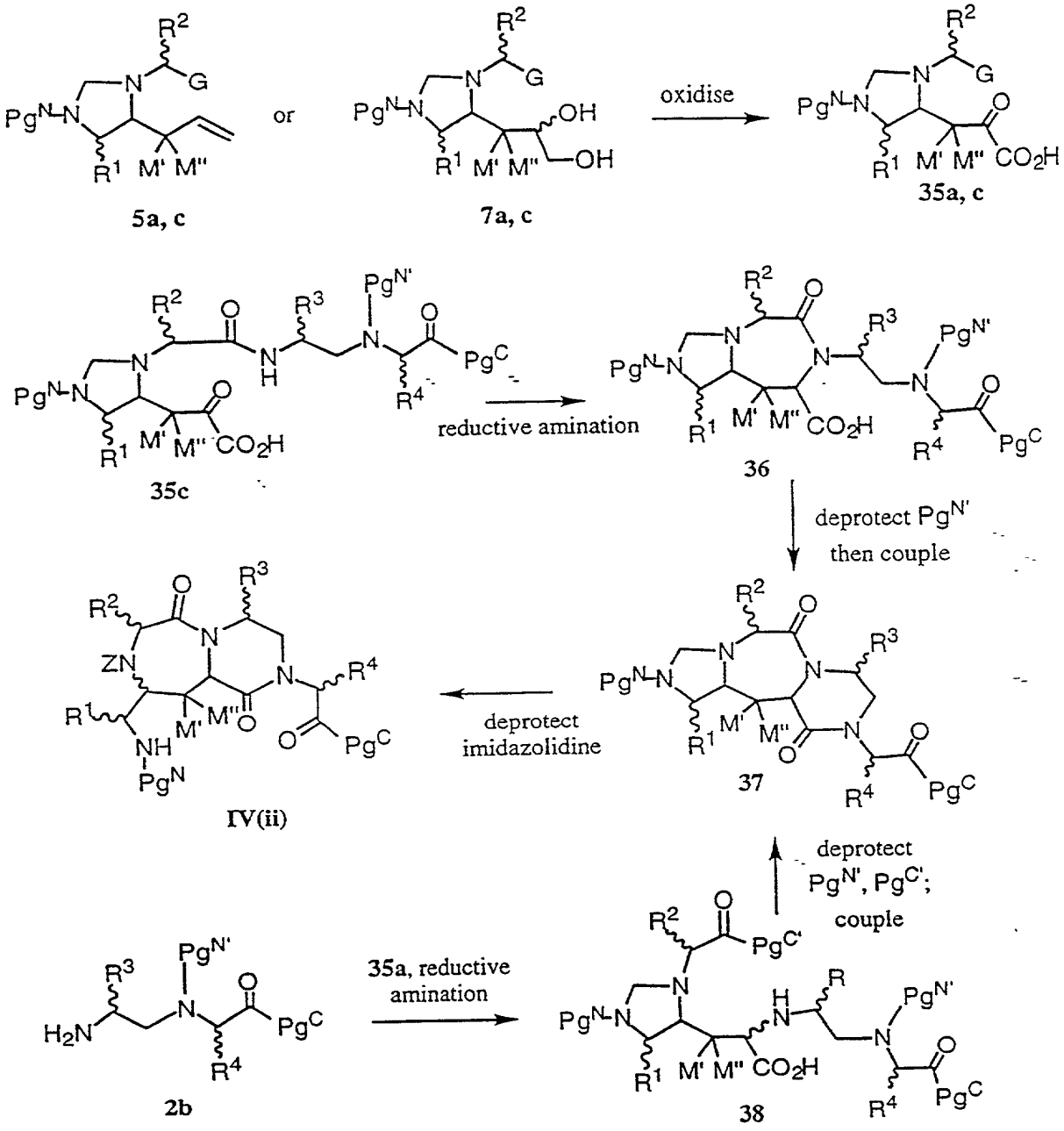
Scheme 11. Synthesis of beta buldge mimic **III(i)** using the general method for the synthesis of **II(i)** (as described in Scheme 5).

SCHEME 12



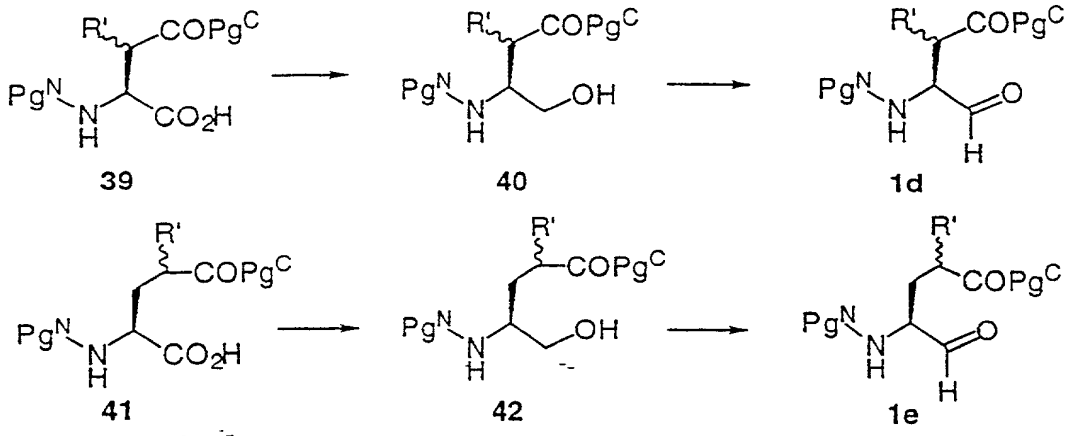
Scheme 12. Synthesis of bicyclic β-turn mimetic systems IV(i).

SCHEME 13

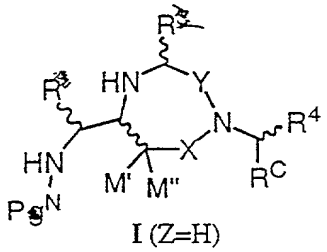


Scheme 13. Synthesis of bicyclic beta turn mimetic systems IV(ii).

SCHEMES 14 AND 15

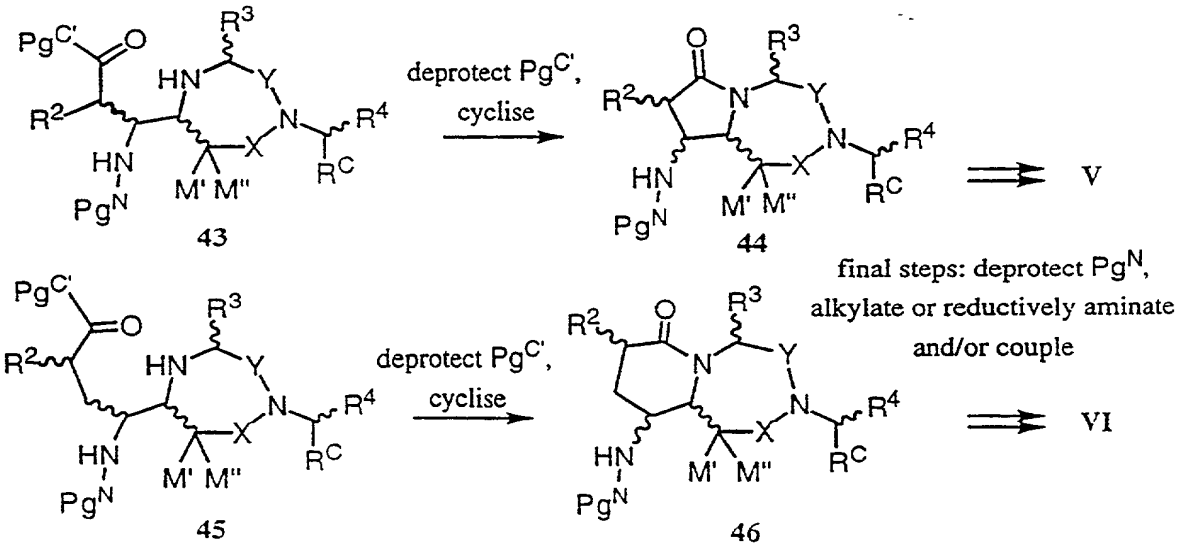


Scheme 14. Alkylated aspartic and glutamic acid derivatives. See text for methods.



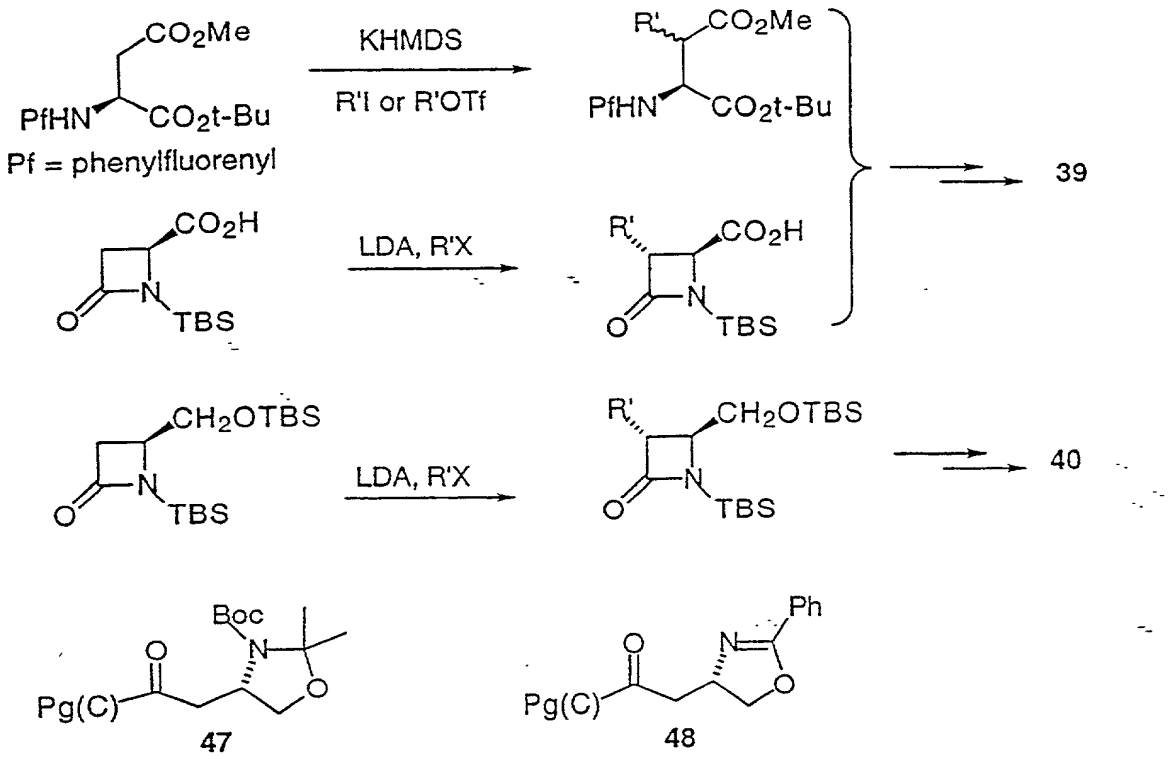
I (Z=H)

	X	Y
I(i)	CH(M)	C(O)
I(ii)	C(O)	CH_2



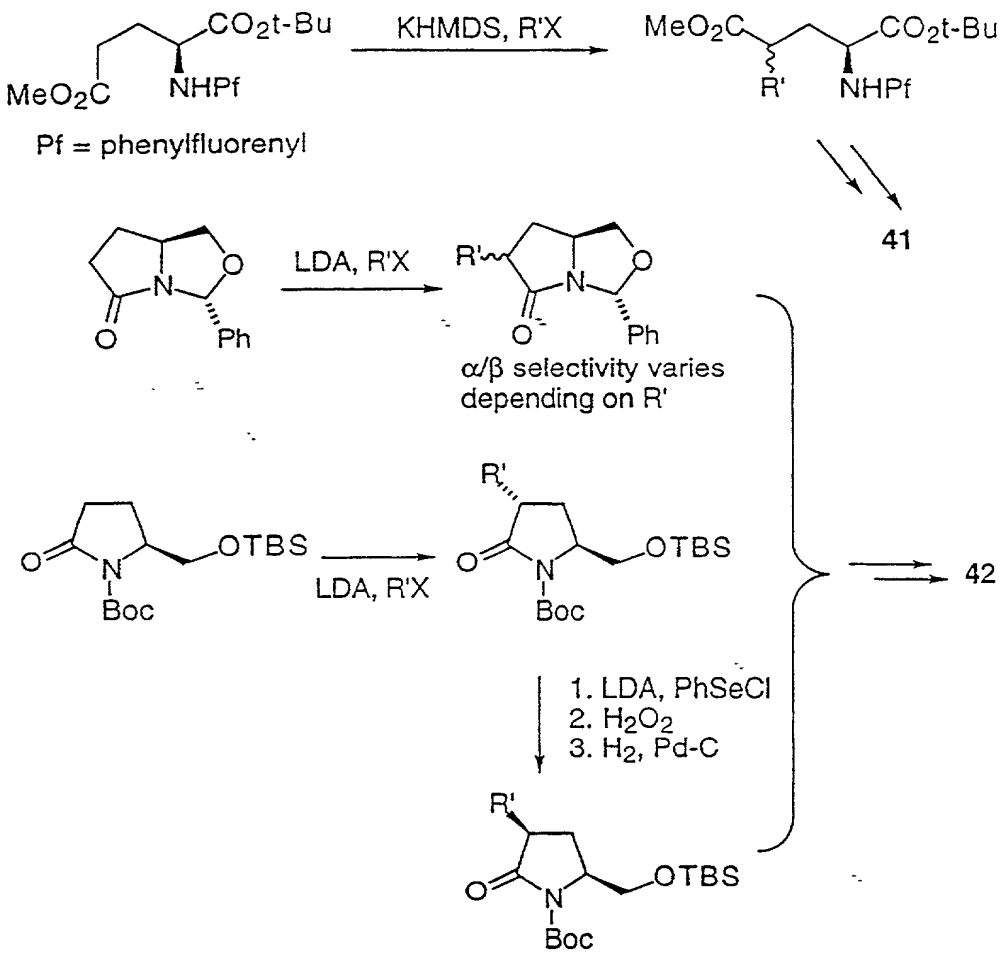
Scheme 15. Synthetic methods for the neutral bicyclic β-turn mimetics **V** and **VI**.

SCHEME 16



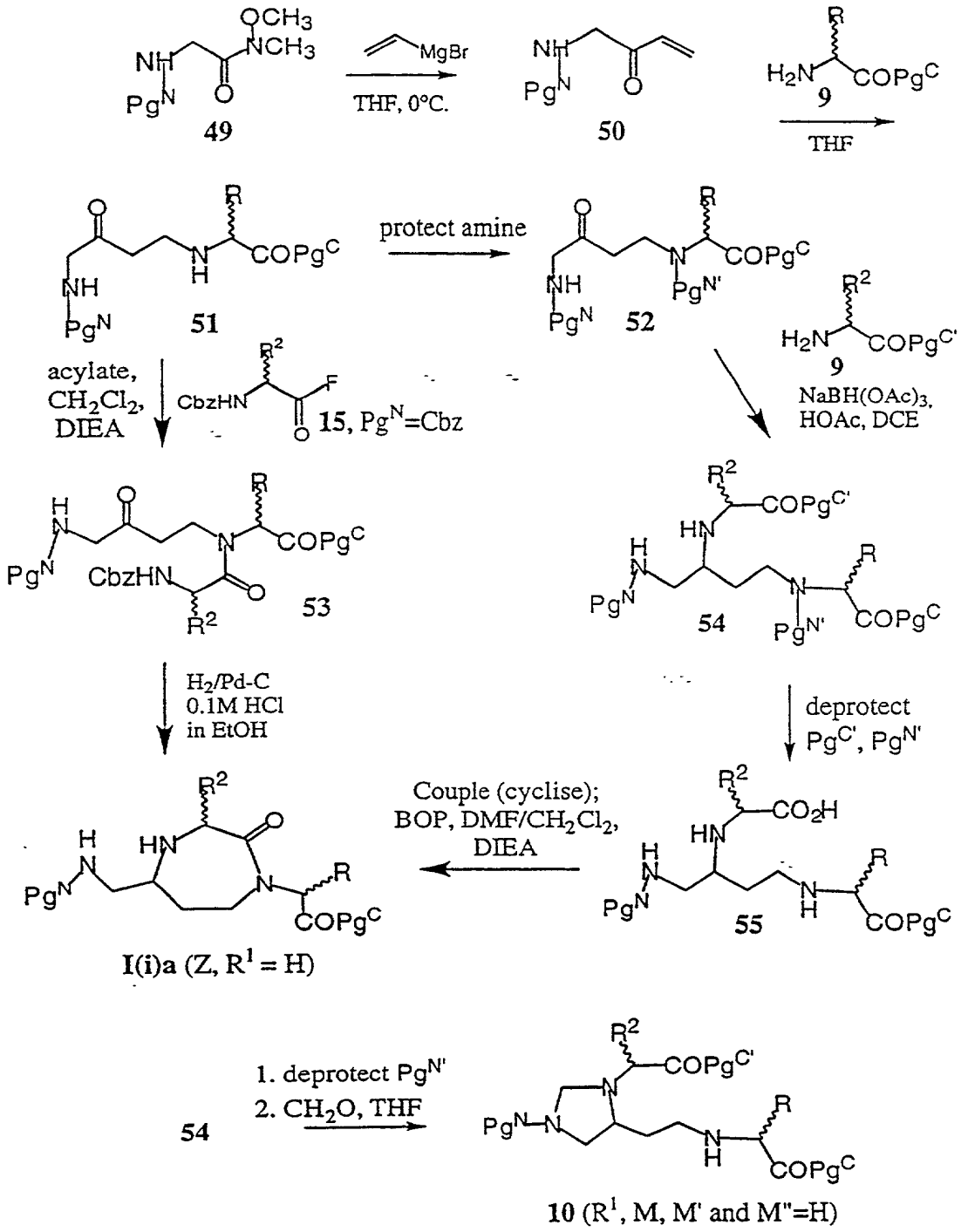
Scheme 16. Alkylation of aspartic acid derivatives.

SCHEME 17



Scheme 17. Alkylation of glutamic acid derivatives.

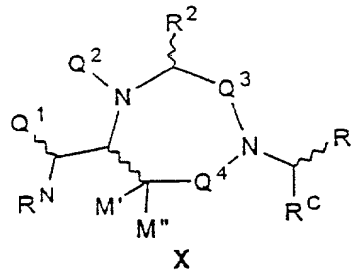
SCHEME 18



Scheme 18. Shorter procedure for the preparation of **10** and **I(i)a** where R^1 is hydrogen.

CLAIMS

1. A general mimetic of the structure



X

wherein:-

~ indicates a bond at a chiral centre of the structure which centre may be in the R or S configuration or a mixture thereof;

R and R^2 is an amino acid side chain group which may be the same or different;

M^I and M^{II} may be the same or different and are selected from the group consisting of hydrogen, C_1-C_4 alkyl, chloro and C_1-C_4 alkoxy;

R^N is $-N(Z^I)PgN$ where Z^I is selected from the group consisting of hydrogen, methyl and part of a cyclic amino acid sidechain joined to Q^I and PgN is a protecting group for amine;

R^C is selected from the group consisting of a carboxy terminal part of the mimetic, hydrogen, R and $-CH_2R$;

$Q_1 = R^1$ which has the same definition as R and R^2 above and Q_2 = Z where Z is selected from the group consisting of hydrogen, methyl, ethyl, formyl and acetyl, $-CH_2R$, and -C(O)R or alternatively Z is part of a cyclic amino acid side chain group joined to R^2; or Q^1 and Q^2 taken together represent a cyclic group;

Q^3 is selected from the group consisting of Y. -C(O)NHCH(R)Y-, -C(O)ENHCH(R)Y-, $-C(O)N(Q^5)CH(R)Y-$ wherein Y is selected from the group consisting of C(O) and CH_2 and Q^5 is a covalent bond from the Q^4 group to the nitrogen atom in Q^3 to form a bicyclic ring system or alternatively, is selected from the group consisting of hydrogen,

C_1-C_4 alkyl, chloro and C_1-C_4 alkoxy and E is $(AA)_n$ where n is 1-300 and AA is an amino acid residue; and

Q^4 is selected from the group consisting of $CH(M^I)$, C(O), $CH(Q^5)CH_2$ and $CH(Q^5)$ C(O);

with the provisos that when:-

(i) $Q^4 = CH(M^I)$, Y is C(O);

(ii) Q^4 = C(O), Y is CH_2;

(iii) $Q^4 = CH(Q^5)CH_2$, Y is C(O);

(iv) $Q^4 = CH(Q^5)C(O)$, Y is CH_2;

(v) $Q^3 = -C(O)N(Q^5)CH(R)Y$, Q^5 is a covalent bond from the Q^4 group to the nitrogen atom in Q^3 which is a cyclization forming a bicyclic ring system.

2. A peptide mimetic as claimed in Claim 1 wherein when Q_1 and Q_2 form a cyclic group Q_1Q_2 which is selected from the group consisting of -CH(R)C(O)-, $-CH_2CH(R)C(O)-$, $-CH_2CH_2CH(R)C(O)-$, $-CH(R)CH_2-$, $-CH_2CH(R)CH_2-$, $-CH_2CH_2CH(R)CH_2-$, $-CH_2CH(R)-$, $CH_2CH_2CH(R)-$, $-CH(R)CH_2CH_2-$, $-CH_2CH(R)CH_2CH_2-$, $CH(R)CH_2C(O)-$ and $-CH_2CH(R)CH_2C(O)-$.

3. A peptide mimetic as claimed in Claim 1 wherein n is 1-30.

4. A peptide mimetic as claimed in Claim 1 wherein E represents a loop of n amino acids which additionally incorporate non-alpha amino acid(s), alpha dialkyl amino acid(s) or other amino acid which provides the peptide mimetic with increased binding affinity or increased ease of detection, identification or purification.

5. A peptide mimetic as claimed in Claim 1 wherein Q^1 is R, Q^2 is Z, Q^3 is Y.

6. A peptide mimetic as claimed in Claim 1 wherein Q^1 is R, Q^2 is Z, Q^3 is C(O)NHCH(R)Y and Q^5 is M^I.

7. A peptide mimetic as claimed in Claim 1 wherein Q^1 is R, Q^2 is Z, Q^3 is C(O)NHCH(R)C(O)-NHCH(R)Y and Q^5 is M^I.

8. A peptide mimetic as claimed in Claim 1 wherein Q^1 is R, Q^2 is Z, Q^3 is $C(O)N(Q^5)CH(R)Y$ and Q^5 is a covalent bond to Q^3.

9. A peptide mimetic as claimed in Claim 1 wherein Q^1 is $CH(R)C(O)Q^2$, Q^2 is a covalent bond to Q^1, Q^3 is Y and Q^5 is M^I.

10. A peptide mimetic as claimed in Claim 1 wherein Q^1 is $CH_2CH(R)C(O)Q^2$, Q^2 is Q^1, Q^3 is Y and Q^5 is M^I.

11. A peptide mimetic as claimed in Claim 1 wherein R^C is $C(O)Pg^C$ where Pg^C is a protecting group for carboxylic acid.

12. A peptide mimetic as claimed in Claim 11 wherein Pg^C is selected from the group consisting of alkoxy, benzyloxy, allyloxy, fluorenyl methyloxy, amines forming easily removable amides, a cleavable linker to a solid support, the solid support, hydroxy or NHR R, C(O)R or the remaining C-terminal portion of the mimetic.

13. A peptide mimetic as claimed in Claim 12 wherein PgC is methoxy or ethoxy.

14. A peptide mimetic as claimed in Claim 1 wherein Pg^N is a protecting group for an amine.

15. A peptide mimetic as claimed in Claim 1 wherein Pg^N is selected from the group consisting of Boc, Cbz, Fmoc, Alloc, trityl, a cleavable linker to a solid support, the solid support, hydrogen, R, CO(R) or part of the remaining N terminal portion of the mimetic.

16. A peptide mimetic as claimed in Claim 1 wherein M^I or M^{II} is methoxy.

17. A peptide mimetic as claimed in Claim 1 wherein M^I or M^{II} is methyl.

18. Compounds I(i)a herein.

19. Compounds I(i)a herein where R_1 and $R_2 \neq H$.

20. Compounds I(ii)a herein.

21. Compounds I(ii)a herein where R_1 and $R_2 \neq H$.

22. Compounds II(i)a herein.

23. Compounds II(i)a herein where R_1 and $R_2 \neq H$.

24. Compounds II(iii)a herein.

25. Compounds II(iii)a herein where R_1 and $R_2 \neq H$.

26. Compounds III(i)a herein.

27. Compounds III(iii)a herein.

28. Compounds IV(i)a herein.

29. Compounds IV(ii)a herein.

30. Compounds V(i)a and V(ii)a herein.

31. Compounds VI(i)a and VI(ii)a herein.

32. Compounds 4a-d herein.

33. Compounds 5a-d herein.

34. Compounds 6a-d herein.

35. Compounds 7a-d herein.

36. Compounds 8a-d herein.

37. Compounds 4a-d herein where R^1 and $R^2 \neq H$.

38. Compounds 5a-d herein where R^1 and $R^2 \neq H$.

39. Compounds 6a-d herein where R^1 and $R^2 \neq H$.

40. Compounds 7a-d herein where R^1 and $R^2 \neq H$.

41. Compounds 8a-d herein where R^1 and $R^2 \neq H$.

42 Compounds 10 herein or compounds 10 where R^1 and $R^2 \neq H$.

43. Compounds 11-14, 16-19, 21-22, 23(a-d), 25(a-d), 26-34, 35(a-c), 36-38 and 43-46 or compounds 11-14, 16-19, 21-22, 23(a-d), 25(a-d), 26-34, 35(a-c), 36-38 and 43-46 where R^1 and $R^2 \neq H$.

44. A process for preparation of compounds 4a-d herein comprising the reaction of imines 3a-d herein with an allyl boron reagent to provide compounds 4a-d.

45. A process as claimed in Claim 44 wherein imines 3a-d are prepared by condensation of amino acid aldehydes 1 herein and amines 2a-d herein.

46. A process as claimed in Claim 44 wherein addition of formaldehyde solution to compounds 4a-d provides imidazolidines 5a-d herein.

47. A process as claimed in Claim 46 wherein compounds 6a-d herein are obtained by oxidation of imidazolidines 5a-d.

48. A process as claimed in Claim 46 wherein imidiazolidines 5a-d are dihydroxylated to provide compounds 7a-d herein.

49. A process as claimed in Claim 46 wherein aldehydes 8a-d herein are obtained by ozonlysis of imidazolidines 5a-d.

50. A process as claimed in Claim 48 wherein aldehydes 8a-d are obtained by oxidation of compounds 7a-d.

51. A process as claimed in Claim 48 wherein compounds 6a-d are reduced to form aldehydes 8a-d.

52. A process as claimed in Claim 50 wherein aldehydes 8a-d are oxidized to provide carboxylic acids 6a-d.

53. A process as claimed in Claim 50 wherein aldehydes 8a are subjected to reductive amination with compound 9 herein to provide amines 10 herein.

54. A process as claimed in Claim 53 wherein amines 10 are subjected to removal of group PgC^1 to provide compounds 11 herein.

55. A process as claimed in Claim 54 wherein compounds 11 are subjected to cyclization to provide compounds 12 herein.

56. A process as claimed in Claim 55 wherein mimetics I(i) herein are obtained by hydrogenation of compounds 12.

57. A process as claimed in Claim 55 wherein mimetics I(i)a herein are produced by acid hydrolysis of compounds 12.

58. A process as claimed in Claim 47 wherein mimetics I(ii) are obtained by:-

(i) removal of group PgA^1 from compounds 6b to provide compounds 13 herein;

(ii) cyclization of compounds 13 to provide compounds 14 herein; and

(iii) deprotection of the imidazolidine group in compounds 14.

59. A process as claimed in Claim 53 wherein amines 10 are reacted with compounds 15 herein in the presence of base to provide compounds 16 herein, whereby groups PgN^1 and PgC^1 are subsequently

removed to provide compounds 17 herein which, after hydrogenation and cyclization, provide mimetics II(i) herein.

60 A process as claimed in Claim 47 wherein compounds 6c have the group PgN^1 removed to provide compounds 18 herein which are converted to compounds 19 herein which by deprotection of the imidazolidine group are converted to mimetics II(ii) herein.

61 A process as claimed in Claim 47 wherein compounds 6a are reacted with compound 20 herein to provide compound 21 herein which, after removal of groups PgN^1 and PgC^1 are converted to compounds 22 herein which are subsequently converted to compounds 19 which by deprotection of the imidazolidine group, are converted to mimetics II(ii) herein.

62. A process as claimed in Claim 46 wherein compounds 5a-d are converted to compounds 23a-d herein by hydroboration whereafter compounds 23a-d are oxidized to compounds 24a-d herein whereafter compound 24a is subjected to reductive amination with compound 9 to provide compounds 26 herein which are subsequently converted to mimetics II(iii) herein.

63. A process as claimed in Claim 46 wherein compounds 5a-d are converted to compounds 23a-d herein by hydroboration whereafter compounds 23a-d are oxidized to form compounds 25a-d herein and subsequently compound 25a or 25c is converted to mimetics II(iv) herein.

64. A process as claimed in Claim 53 wherein amines 10 are reacted with compounds 15 herein which compounds in the presence of base are converted to compounds 16 herein which then have the group PgN^1 removed to provide compounds 27 herein which after reaction with compound $PgN^1NHCH(R)COOH$ are converted to compounds 28 herein which are subsequently converted to mimetics III(i) herein.

65. A process as claimed in Claim 48 wherein compound 7a is dehydrated to provide compound 29 herein which are then converted to compound 30 herein whereafter compounds 30 by reaction with compound $PgN^1NHCH(R)COOH$ form compounds 31 which are then

oxidized to form compounds 32 herein which after removal of groups PgN^I and PgC^I and reductive animation are converted to compounds 33 herein which are subsequently converted to compounds 34 herein which after deprotection of the imidazolidine group is converted to mimetics IV(i) herein.

66. A process as claimed in Claim 46 or 48 wherein compounds 5a, c or 7a, c are oxidized to form compounds 35a, c herein whereafter compounds 35c are subjected to reductive animation to form compounds 36 herein which after removal of the group PgN^I are converted to compounds 37 herein whereafter mimetics IV(ii) are produced by deprotection of the imidazolidine group.

67. A process as claimed in Claim 46 or 48 wherein compounds 5a, c or 7a, c are oxidized to form compounds 35a, c herein whereafter compounds 35c are reacted with compounds 26 herein to form compounds 38 which after removal of the groups PgN^I and PgC^I are converted to compounds 37 which after deprotection of the imidazolidine are converted to mimetics IV(ii).

68. A process as claimed in Claim 57 wherein mimetics I(i) wherein R^1 is an alkylated aspartate or alkylated glutamate side chain which correspond to compounds 43 and 45 respectively which subsequently each have the group PgC^I removed and cyclized to provide compounds 44 and 46 respectively which are subsequently converted to mimetics V and VI respectively.

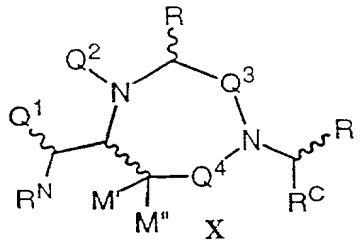
69. A process of making compounds 54 herein wherein initially compounds 49 herein are converted to compounds 50 herein which thereafter after reaction with compounds 9 herein produces compounds 51 herein which are subsequently converted to compound 52 herein which are then reductively aminated with compounds 9 to provide said compounds 54.

70. A process as claimed in Claim 69 wherein compounds 54 are converted to compounds 55 after removal of groups PgC^I and PgN^I which are then converted to mimetics I(i)a where Z and R^I is H.

71. A process as claimed in Claim 69 wherein compound 54 after removal of PgN^{I} is converted to compounds 10 herein wherein R^{I}, M, M^{I} and M^{II} are H.

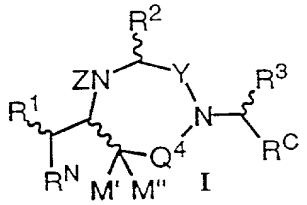
72. A process for making mimetics I(i)a herein stereospecifically wherein compounds 49 herein are reacted with vinyl magnesium bromide to compounds 50 herein which are then reacted with compounds 9 herein to form compounds 51 herein which are then reacted with compounds 15 herein wherein PgN^{I} is Cbz to form compounds 53 herein which are then converted to mimetics I(i)a by hydrogenation.

73. A library of peptide mimetics comprising at least one mimetic from any one of Claims 1-31.



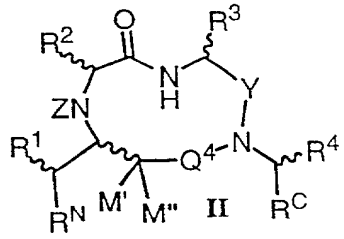
	Q^4	Y
(i)	-CH(M)-	C(O)
(ii)	-C(O)-	CH_2
(iii)	$-CH(Q^5)CH_2-$	C(O)
(iv)	$-CH(Q^5)C(O)-$	CH_2

X



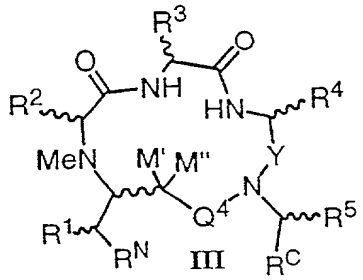
I

	Q^4	Y
I(i)	CH(M)	C(O)
I(ii)	C(O)	CH_2



II

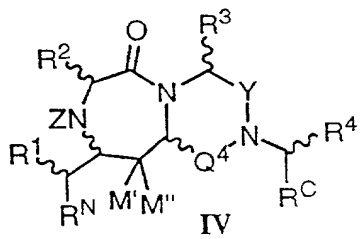
	Q^4	Y
II(i)	CH(M)	C(O)
II(ii)	C(O)	CH_2
II(iii)	$CH(M)CH_2$	C(O)
II(iv)	CH(M)C(O)	CH_2



III

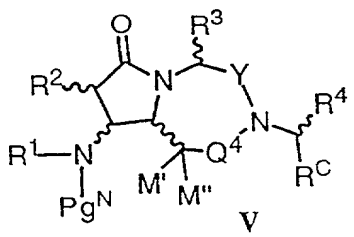
	Q^4	Y
III(i)	CH(M)	C(O)
III(ii)	C(O)	CH_2
III(iii)	$CH(M)CH_2$	C(O)
III(iv)	CH(M)C(O)	CH_2

Figure 1. General structure of the mimetic systems and preferred cyclic turn and loop mimetic systems. Refer to the main text for a full description of the Q, R, Pg, Z and M groups.



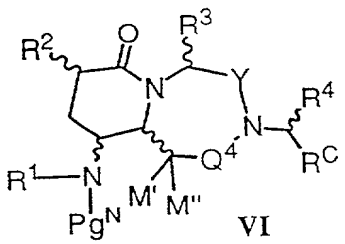
IV

	Q^4	Y
IV(i)	CH_2	C(O)
IV(ii)	C(O)	CH_2



V

	Q^4	Y
V(i)	CH(M)	C(O)
V(ii)	C(O)	CH_2



VI

	Q^4	Y
VI(i)	CH(M)	C(O)
VI(ii)	C(O)	CH_2

Figure 2. Bicyclic beta turn mimetic systems. Refer to the main text for a full description of the R, Pg, Z and M groups.

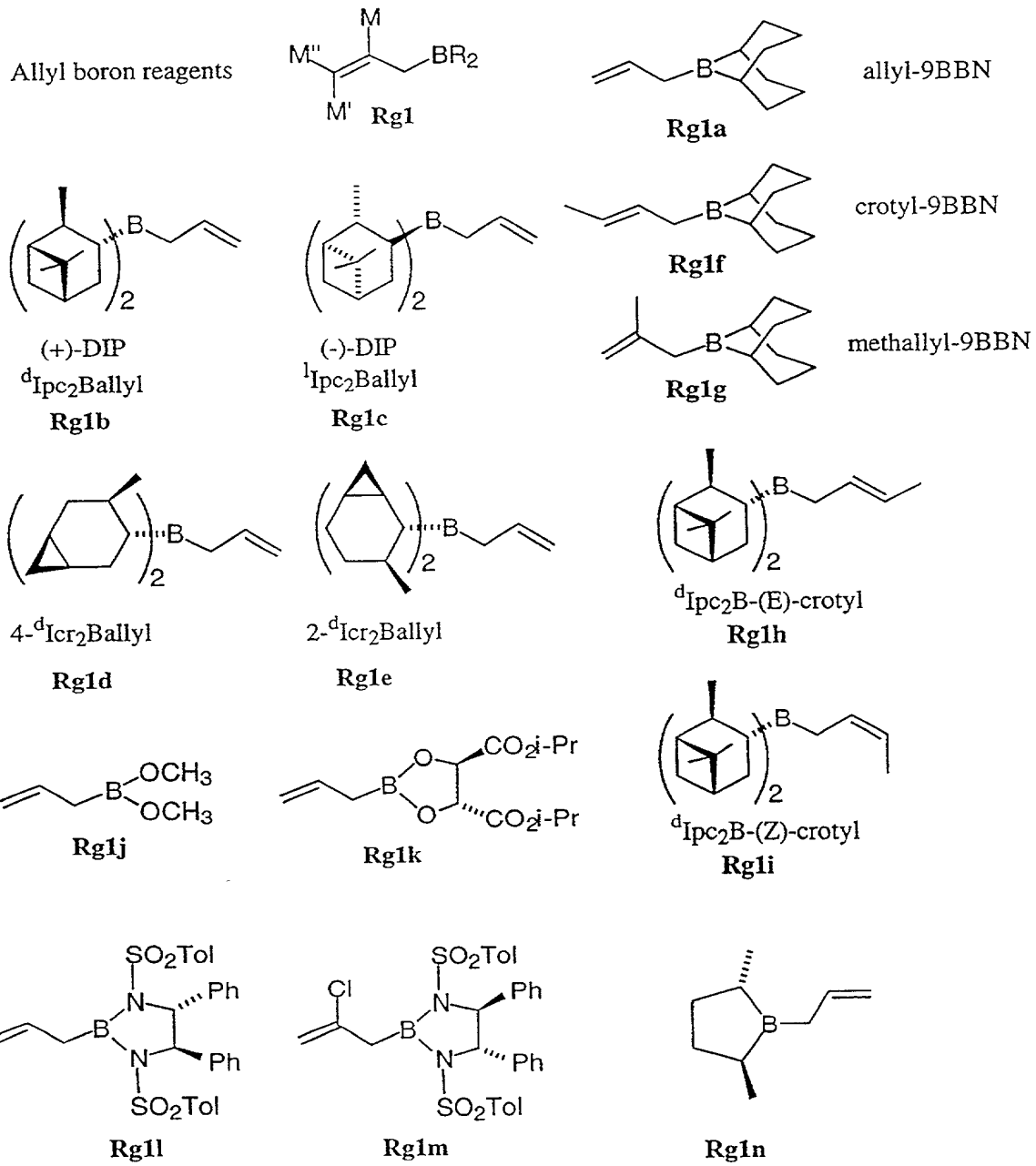


Figure 3. Selected allylboron reagents

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	080056-000200US
First Named Inventor	Peter J. Cassidy
COMPLETE IF KNOWN	
Application Number	/
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PEPTIDE TURN MIMETICS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) March 24, 1999 as United States Application Number or PCT International Application Number PCT/AU99/00207 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
PP2548	Australia	3/18/1998	☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*
OR
☒ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
Kevin L. Bastian	34,774		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] *OR* ☒ Correspondence address below

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Country	US	Telephone	415-576-0200	Fax	415-576-0300

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Peter Joseph	Cassidy

Inventor's Signature						Date	8/12/00
Residence: City	~~XXXXXX~~ Ashgrove	State	QLD	Country	Australia	Citizenship	AU
Post Office Address	~~32 Chiswick Road~~ 24 Cavell Terrace						
Post Office Address							
City	Ashgrove	State	QLD	ZIP	4060	Country	Australia

☒ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])		Family Name or Surname					
Peter Alan		Hunt					
Inventor's Signature	[signature] GBX				Date	4/Dec/00	
Residence: City	Harlow, Essex	State		Country	UK	Citizenship	UK
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Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])		Family Name or Surname					
Paul Francis		Alewood					
Inventor's Signature	[signature] AUX				Date	22/12/00	
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Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor						
Given Name (first and middle [if any])		Family Name or Surname					
Tracie Elizabeh		Ramsdale					
Inventor's Signature	[signature] AUX				Date	20/12/00	
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City	Tarragindi	State	QLD	ZIP	4065	Country	Australia

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